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PHOTO-ORGANO-CATALYSIS FOR SUSTAINABLE REDOX CHEMISTRY

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PHOTO-ORGANO-CATALYSIS FOR SUSTAINABLE REDOX CHEMISTRY

Matthew Camilleri

A thesis submitted for the degree of Masters of Philosophy

Supervisor: Dr. Dave Carbery

Department of Chemistry

August 2019

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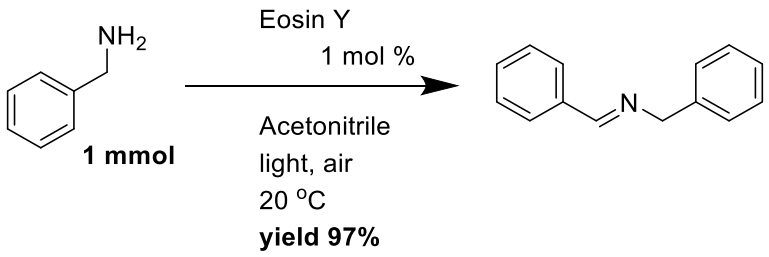
Abstract

Solar photocatalysis is a field of chemistry which is increasing in popularity for use in chemical production. This field has so far been dominated by transition metal complexes, and whilst these can give a variety of products in good yields their sustainability remains an issue. Ruthenium and iridium complexes are problematic due to their scarcity, high price and toxicity. As alternatives to using these complexes organic molecules can be used. These include flavins and Eosin Y, the former being natural molecules whilst the latter is a synthetic dye. These molecules have shown promise in producing a radical on a benzylic carbon.

The photocatalytic ability of Eosin Y was investigated in the dehydrogenative coupling of amines as seen in scheme 1.



Scheme 1: The dehydrogenative coupling of benzylamine using Eosin Y as a photocatalyst.

This oxidative coupling gave very good yields showing good reactivity even with secondary amines, in contrast to previous studies that have been done on the dehydrogenative coupling reactions. Additionally, mechanistic studies have been carried out on the photocatalytic reaction of benzylamine, supporting the proposed mechanism involving a one electron oxidation of benzylamine, which was also in agreement with literature.

Acknowledgements

I would like to express my sincere gratitude towards all the people who helped me throughout my academic journey, especially during the course of this thesis. This study marks the end of an incredible four-year experience within the University of Bath.

My appreciation extends to all the members of the CSCT cohort 13 who supported me throughout this journey and made life fun, full of laughs and worth living. I would also like to thank the staff of the CSCT with special thanks to Ms Rubina Kalra who helped mw in whatever I needed, be it academic or personal.

Words can never express my gratitude towards my parents and role models, Victor and Carmen and my sisters, for constantly supporting me and encouraging me to be better. I would also like to thank my girlfriend Chiara for always being by my side, for her patience, guidance and suggestions for improvement.

Lastly, I would like to thank God for giving me the strength to reach my dreams, and courage to overcome all obstacles, no matter how impossible they seemed.

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Abbreviations

Bipy – 2,2’-bipyridine

c – speed of light in the vacuum

d – doublet

DMF – dimethylformamide

DMSO – dimethyl sulfoxide

Et – ethyl

h – Planck’s constant

Hz – hertz

J – coupling constant

LED – light emitting diode

m – multiplet

Me – methyl

NMR – nuclear magnetic resonance

Nuc – nucleophile

r – radius

rt – room temperature

s – singlet

T – temperature

TEMPO – 2,2,6,6-tetramethyl-1-piperinidinyloxyl

UV – ultraviolet

UV/Vis – ultraviolet/visible light

Wm^{-2} – watts per square metre

δ – chemical shift

λ – wavelength

ν - frequency

Chapter One
Introduction

The demand for energy worldwide being on the increase and the effect of burning fuel having its toll on the atmosphere, it is important to find alternative sustainable technologies that can be used for generations to come. Sunlight is a unique natural resource; it is a free, non polluting, abundant inexpensive source of energy. With increasing environmental consciousness, finding ways of how to harness the energy of solar radiation and storing excess energy is becoming more crucial.

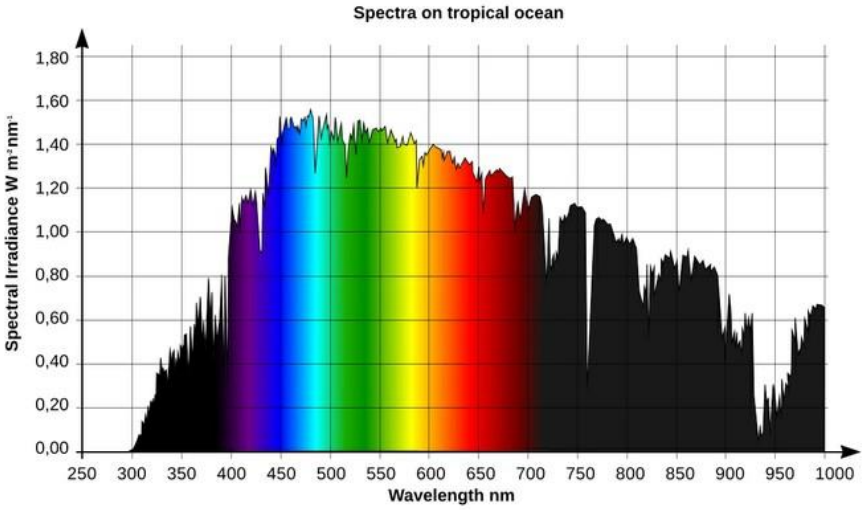


Figure 1: the electromagnetic radiation from the sun as taken from
http://www.cvreefers.org/showthread.php?24813-The-Importance-of-Lighting-Spectrum

Harnessing solar energy through photovoltaics is an area of research that has become a massive field in chemistry, and a number of advancements have been made in recent years in order to be able to increase the efficiency of such technology[1,2]. Whilst photovoltaics are very powerful as a tool, they do not give the opportunity to store excess energy, meaning that it can only be used whilst the sun is shining, and other energy sources would be needed for when no sun is available.

Research on the idea of using solar energy and storing it as energy in chemical bonds has been around since the early 20th century[3]. The first step was discovering that visible light can be used to photo-excite organic chemical reactions, which gave pioneers in the area a way to convert light into chemical energy, which in turn creates the possibility of representing an inexhaustible source of clean renewable energy.

All fossil fuels that are currently being used have been produced directly from sunlight, and this is mainly due to the process of photosynthesis, which is nature's way of changing light energy into chemical energy. Photosynthetic organisms are the basis of all life, as these are

always found at the bottom of any food chain in nature. This extraordinary process has been developed over millions of years through evolution, but this idea can be used to try and replicate the process in a lab.

Mimicking photosynthesis has been a challenge for chemists, biologists and physicists alike.[4] The process of using light activation opens up a whole new area of chemistry that has until now not been very well understood.

1.1 What is Photochemistry?

Photochemistry is a branch of chemistry that focuses on the chemical effects of light. Different molecules interact with light differently, and this in turn changes the reactivity of such molecules.[5]

When talking about photochemistry it is important to understand which interactions are possible, and these can be explained using a Jablonski diagram. A Jablonski diagram illustrates the electronic states inside a molecule and the transitions between them. A molecule can absorb a photon of light exciting an electron from the lowest energy configuration, which would be the lowest electronic state, to a higher energy configuration. These excitations are only possible when an electron absorbs the exact frequency it requires to reach a higher energy level. Each energy level is further divided into small bands called vibrational levels. When an electron is excited from its ground state to a higher energy level it is called absorption, where light is absorbed and the energy is taken up by the electron.

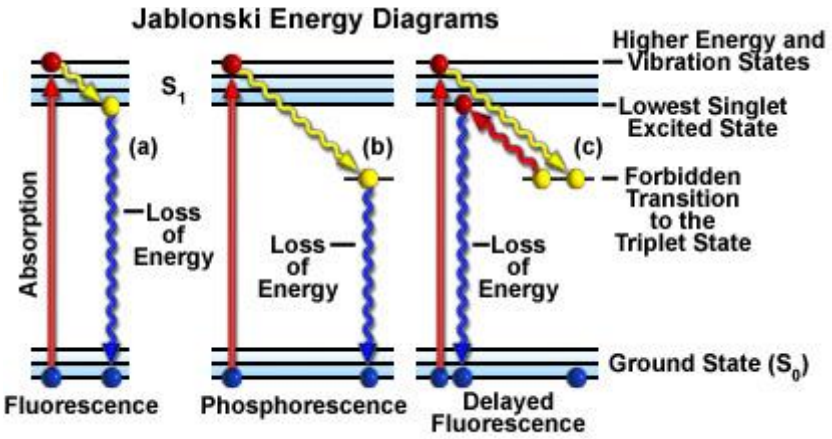


Figure 2: A Jablonski Diagram as taken from
https://micro.magnet.fsu.edu/primer/java/jablonski/lightandcolor/index.html

Once the electron is excited it will undergo vibrational relaxation to get to the lowest energy level of its new energy state, from which it can undergo two different processes; fluorescence or internal conversion. Fluorescence occurs when the electron goes directly down from an

excited level to the ground state. On the other hand internal conversion is when the electron changes from a singlet to a triplet instead of de-exciting to the ground state immediately. This means that the excited electron changes its spin so that the molecule would has two electrons of the same spin.

Photochemistry follows two rules, being the; orbital overlap selection rule and spin selection rule. Orbital overlap selection describes the spatial overlap between the ground state and the excited state, with more overlap making the excitation of the electron from the ground state to an excited state easier. The spin selection rule states that for a transition to take place the multiplicity of the molecule has to remain the same with intersystem crossing being very slow, as this is a forbidden transition.

1.2 Why use Photochemistry?

Photochemistry is an area of chemistry that is currently finding a new renaissance, especially in the use of visible light. Visible light can be considered as one of the most sustainable resources, being available on a daily basis all throughout the world. This enables chemists to be able to introduce functionalities at much milder conditions than at what is currently being used under thermal conditions.

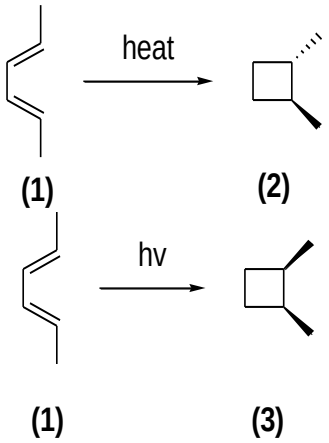
Woodward Hoffmann rules, devised to predict pericyclic reactions in organic chemistry reactions have been known to forbid certain reactions from taking place under thermal conditions. These rules were first formulated to explain stereospecificity of pericylcic ring opening and ring closing reactions at the termini of open chain conjugated polyenes both when using thermal reactions or photochemical reactions.

The Woodward Hoffmann rules are as follows[6,7]:

- In an open-chain system containing 4n-electrons, the orbital symmetry of the highest occupied molecule orbital is such that a bonding interaction between the termini must involve overlap between orbital envelopes on opposite faces of the system and this can only be achieved in a conrotatory process.

- In open systems containing 4n + 2 electrons, terminal bonding interaction within ground-state molecules requires overlap of orbital envelopes on the same face of the system, attainable only by disrotatory displacements.

- In a photochemical reaction an electron in the highest occupied molecular orbital (HOMO) of the reactant is promoted to an excited state leading to a reversal of terminal symmetry relationships and reversal of stereospecificity.



Scheme 2: The difference between the products of a diene using photochemistry or thermal chemistry, following the Woodward-Hoffmann rules.

1.3 The Solar Spectrum and Light as an Energy Source

All mass-containing objects with a temperature of greater than absolute zero emit radiation, as a product of their surface temperature, as depicted by Wein's law[8]. On Earth, most of the radiation is received from the sun, and with a surface temperature of 6000K, the resulting radiation is in the range of infrared, visible and UV.

Visible light is a sub-set of the electromagnetic spectrum and this makes up around 43% of all the radiation that the Earth receives from the Sun making this an invaluable renewable resource.

Quantum theory states that light is quantised, meaning that the energy associated with light is composed of discrete energy pockets called photons. Each individual photon has particle-wave duality, and the energy of each photon can be found using Planck's law (Eqn 1)

$$E = hv$$

Equation 1[5]

Any radiation from the electromagnetic spectrum has the characteristic of travelling at the same speed, c, which is approximately equal to 3 x 10^8 ms^{-1}. The product of the wavelength and frequency for any part of the radiation spectrum is the speed of light, which can be seen in Eqn 2:

$$C = \lambda v$$

Equation 2[5]

From these two equations, relationships between photon energy, frequency and wavelength can be drawn, with energy decreasing as the frequency becomes smaller whilst the wavelength increases.

1.4 Light Matter Interface

When a photon of light is absorbed by an electron, it can cause an electron excitation meaning that an electron jumps from its ground state to a higher energy state, but this can only occur if the energy in the photon is the exact energy required for the electron to jump from the highest occupied molecular orbital to the lowest unoccupied molecular orbital.

Molecular orbitals are limited to holding up to two electrons each; which is better known as the Pauli exclusion Principle, with each of the electrons having a different quantum spin; according to Hund's rule.[5]

The sum of the quantum number gives the total spin angular momentum, denoted as S. This can then be used to determine the number of possible electron orientations, termed as spin multiplicity.

$$S = summation\ of\ m$$

Equation 3[5]

$$Spin\ multiplicity = 2S + 1$$

Equation 4[5]

Spin multiplicity can take a variety of values, but the most common states are the singlet and the triplet state. A singlet state can be described when all the electrons are paired up, and thus these electrons would have a total spin angular momentum of 0 and a multiplicity of 1. The triplet state is when the two electrons have the same angular momentum, and a multiplicity of 3. This description can be seen in Figure 3.

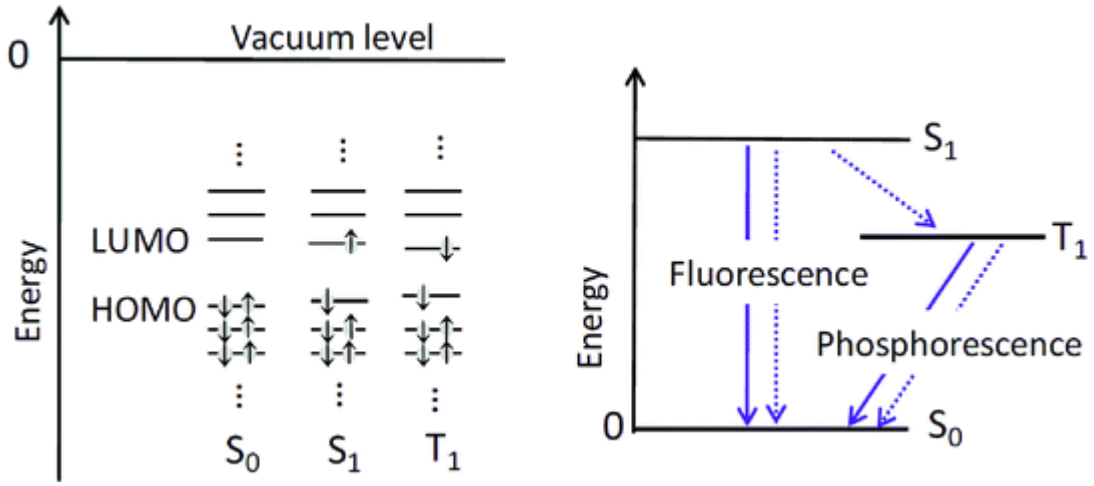


Figure 3: The energy states of a singlet and triplet electron.

1.4.1 Singlet and Triplet State

On excitation from the HOMO to the LUMO the spin multiplicity is maintained, which produces an excited singlet state as this is the only photochemically allowed transition. Once the electron has been excited, the electron can reverse its spin and the multiplicity would change from a singlet to a triplet[5].

On undergoing an electronic excitation the electron is transferred to a different orbital, changing the overall electronic arrangement, which is normally what defines the reactivity of a species. This results in the possibility of the newly excited species behaving completely different from that of the ground state[5].

1.4.2 Vibrational Excitation

An absorption spectrum of a scenario as described with electronic excitation would be a simple line spectrum having a sharp peak where the electron absorbs a photon. This is not what takes place in an absorption spectra as can be seen in Figure 4.

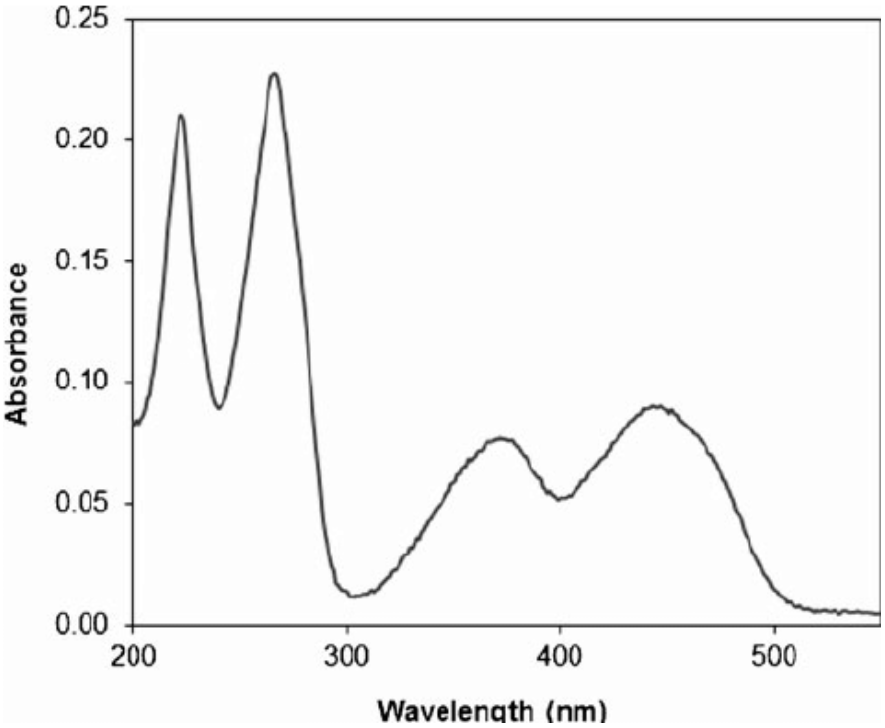


Figure 4: The absorption spectrum of riboflavin in water.[9]

A sharp peak is not present is because each electronic level has a number of vibrational levels, in which electrons can be present. The total energy of a species is comprised of electronic excitation energy, vibrational effects and rotational effects.[5]

The Born-Oppenheimer approximation states that the energy difference between each effect is so substantial that they can be considered to be independent of each other, as depicted in Figure 5.[5]

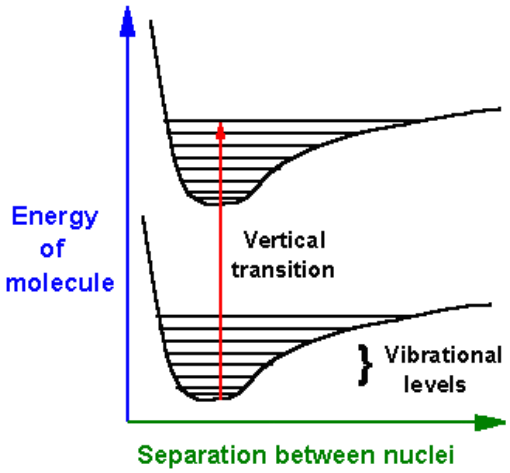


Figure 5: The separation of an energy level into vibrational energies as taken from https://chem.libretexts.org

This results in transitions being established between the ground state and any of the vibrational energy levels within the first excited singlet state, S_1, as seen in Figure 5. Higher energy vibrational states are depicted by use of a higher value, with v = 0 being equivalent to the lowest energy state of an electron level.

1.4.3 Deactivation

Once a triplet state is produced a number of deactivation processes can take place, during which the energy is either dissipated in solution or transferred to another molecule. These processes are illustrated in Figure 7.

Chemistry is bound by the laws of nature, and photochemistry is not any different. The most important rule in photochemistry is the spin selection rule; which refers to transition of electrons from one energy level to the next. The total change in electron spin should be equal to 0.

Transitions that obey this selection rule are said to be spin allowed, whilst others are said to be spin forbidden

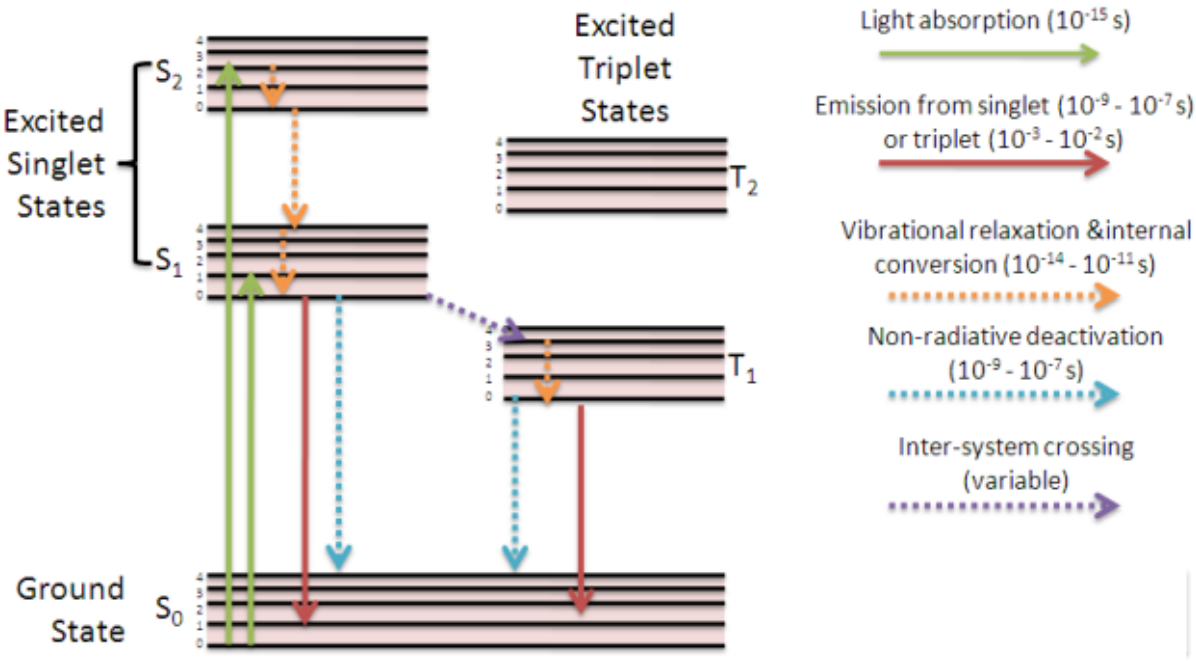


Figure 6: Different transitions with the timescale of each transition on the right as taken from https://chem.libretexts.org

Transitions that do not follow the spin selection rule are said to be forbidden but there are still a number of cases were these still occur. This is because the calculations that derive the rule do not take into account spin-orbital coupling, leading to a mixing of singlet and triplet character.

Excitation may result in an excited species with excess vibrational energy, where v is not equal to 0. Loss of vibrational energy is described as vibrational relaxation, and this mainly occurs when two different molecules collide with each other, in order to obtain the lowest energy of the vibrational state where v = 0. This is a relatively fast process, with a time scale of 10^{-14} – 10^{-11}s.

As a result, all other electronic transitions occur from the lowest energy vibrational state, and can then proceed by emitting energy. Unimolecular emission is a process that only involves one molecule in contrast to bimolecular emission where two molecules are required for the deactivation to take place.

Internal conversion in the relaxation of an excited state to the HOMO, where the electron goes from v = 0 of S_n to an energy equivalent S_1 vibrational level. This is then followed by more vibrational relaxation which is eventually deactivated via luminescence, where a photon of quantified energy is emitted.

Luminescence is divided into two groups; phosphorescent or fluorescent species, based on whether the multiplicity of the excited and ground state are the same or different.

Fluorescent deactivation is a process in which an electronic transition that maintains its overall multiplicity occurs, with the electron deactivating from S_1 to S_0, as shown in Figure 6.

This is a spin allowed transition as the spin multiplicity of this process is 0, and thus this is a very fast process, with a timescale of 10^{-12} to 10^{-6} seconds.

In contrast, phosphorescence occurs when the transition of the electron changes the spin multiplicity of the system, which is forbidden according to the selection rules, and thus this would be very weak and slow.

When an electron manages to change its spin, a triplet state is produced and the process is called intersystem crossing, where the electron jumps from an S_1 v=0 state into a T_1 vibrational state, with the T_1 being lower in energy level than the S_1. The reason why T_1 is lower in energy than S_1 is because of Hund's rule, which states that when two electrons occupy a different orbital the lowest energy state is found when the two electrons have the same quantum number.

As a result, the excited triplet state is always lower in energy than the excited singlet state as shown in Jablonski diagram Figure 2. Similar to the internal conversion this overlap allows for transitions between isoenergetic states, with timescales of 10^{-11} to 10^{-6}s.

Once the triplet state is obtained, deactivation to the ground state follows another forbidden transition, and thus this would be a slow deactivation process with a timescale of 10^{-3} to 10^{-2} seconds. This elongated lifetime is then of sufficient lifetime to allow alternative bimolecular process to directly compete with phosphorescence pathway, which is the basis of photochemistry.

1.5 Photochemistry in Organic Chemistry

1.5.1 Visible light photochemistry

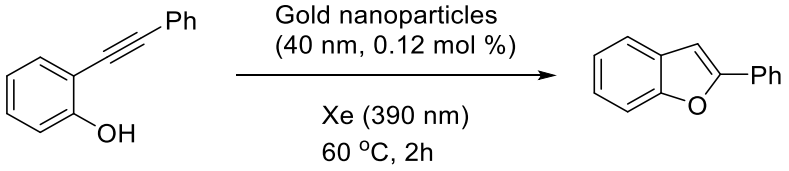
UV light is around 5% of all the light spectrum which the Earth receives from the sun whilst visible light amounts to nearly 45%. This means that if we are to use solar energy as an energy source it would be better if visible light could be harnessed. A lot of research is going into this area, but instead of exciting the molecule itself directly a photocatalyst is being used. A photocatalyst is a compound that absorbs light and then catalyses a different reaction on another compound. A number of such compounds exist, both metal and non-metal based. Chlorophyll is a structure built around magnesium found in nature and is the basis of photosynthesis.

Research in this area has been widely carried out on transition metal complexes of ruthenium and Iridium and it resulted that these are very good in radical chemistry.

For photocatalysis there are two main reaction types: homogenous and heterogeneous; Homogenous catalysis is when the catalyst and the reactant are in the same phase and heterogeneous catalysis is when the catalyst and the reactant are in two different states.

1.5.1.1 Heterogeneous Catalysis

In heterogeneous catalysis the catalyst can normally be recycled much easier than from homogenous catalysis and thus this allows for the use of expensive catalysts such as gold nanoparticles or the introduction of flow chemistry with the catalyst embedded in the reactor and the solution flowing over it[10].



(6) **(7)**

Scheme 3: A catalytic reaction using heterogeneous gold nanoparticles as catalysts and irradiation.

1.5.1.2 Homogeneous Catalysis

Homogeneous catalysis is more common, and whilst both iridium and ruthenium are expensive, various reactions have been developed[11]. Apart from transition metals the use of organic photocatalysts is becoming more commonly used.

1.6 Photocatalysts

The most common photocatalysts are based on transition metal complexes, namely ruthenium and iridium. These metal complexes can act as both reducing and oxidising agents as can be seen in Figure 7. This is all possible because of the change in the electrochemical potential when the triplet state is produced, which can either gain or lose an electron. This can in turn produce a number of reactions that can be used in synthesis[12].

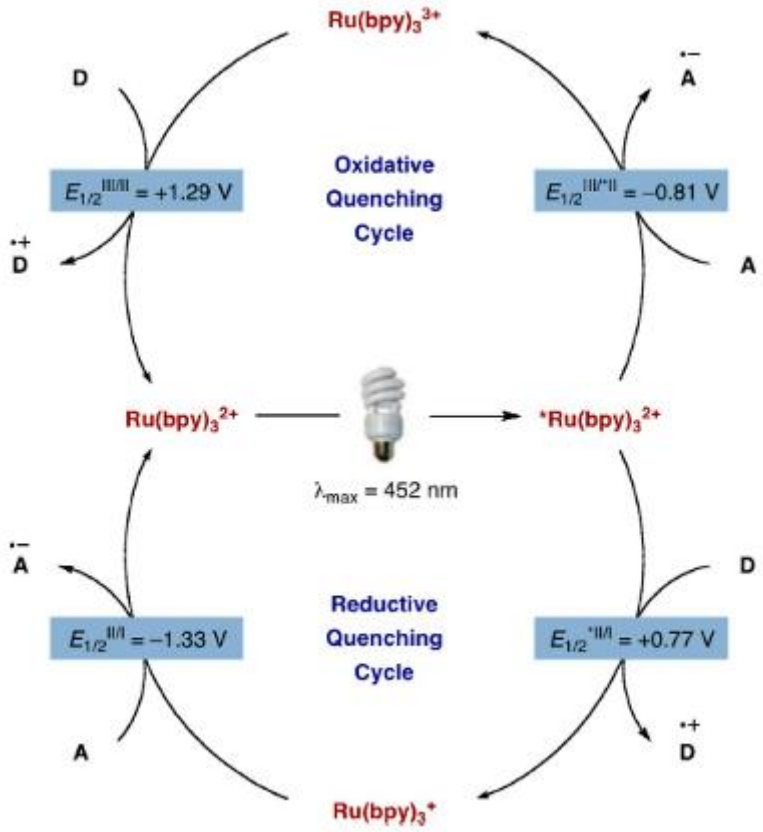


Figure 7: The change in electrochemical potential from the ground state to the excited state[13]

1.6.1 Radical reactions

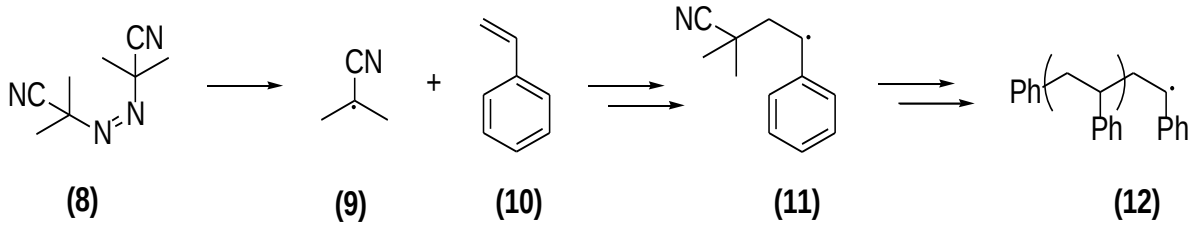
Photoexcitation results in the formation of an excited state, and this can result in some very interesting chemistry that is not always possible under standard reaction conditions; by heating the reaction mixture. Having an in-depth understanding of such a process is crucial for designing a good photochemical reaction.

1.6.1.1 Initiator

A radical can be used to initiate a radical reaction, which play an important role in the preparation of polymers, free radical reactions and in cis/trans isomerisation.

1.6.1.1.1 Polymer reactions

Polyethenes can be initiated using radical reactions, and these would continue to react until either all of the starting material has been consumed by the reaction or else a termination step has taken place. By controlling the amount of the initiator one can control the length and properties of the polymer itself[14].



(8) **(9)** **(10)** **(11)** **(12)**

Scheme 4: A typical radical initiated polymer reaction

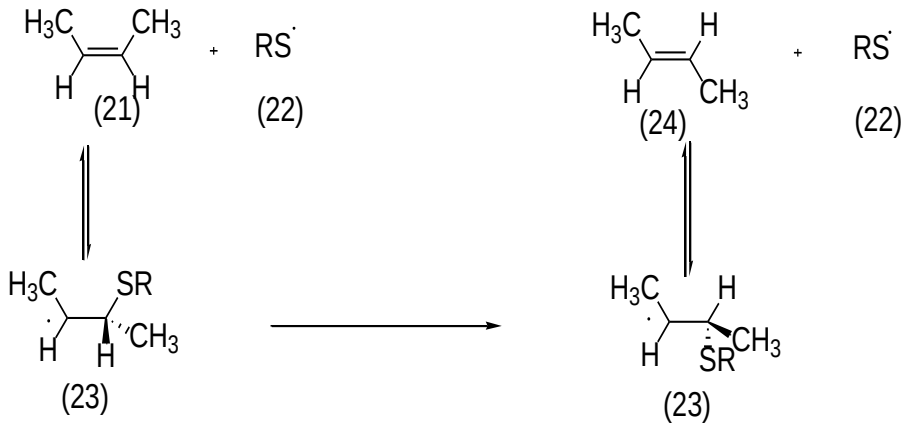
1.6.1.1.2 Free radical reactions

A free radical reaction is a reaction where a free radical is added to a molecule that is not on its own highly reactive, such as an alkane. One of the most common reactions in this area is the substitution of a hydrogen to a halogen in alkane.

Another set of reactions that is initiated and aided by radicals is the free radical addition, mainly halogens which can be added across alkene double bonds, reducing them to alkanes. A similar reaction can take place in the reaction between halogens and alkanes[15].

1.6.1.1.3 Isomerisation

In alkenes the double bond is not free to rotate due to the way the p-orbitals interact together. This means that some alkenes can form two isomers, cis and trans, and it is highly difficult to go from one isomer to the other. If a radical is introduced, the sigma bond would be able to rotate, creating the possibility of having the two isomers upon creation of the double bond again[16].



Scheme 5: Isomerisation of an alkene using radicals

1.6.1.2 Photochemical reactions

An electron can also transfer from one molecule to the other, creating a reactive centre on an atom that is not normally that reactive. In photochemistry the catalyst is in place to create a radical that is then extracted to be used by a different molecule, in a process known as sensitisation.

1.6.1.2.1 Production of fine chemicals with sunlight

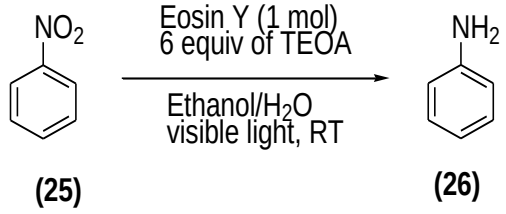
Ruthenium and iridium catalysts are the most commonly used photocatalysts and as such most of the work done in the area has been performed using these two metals. In recent years organo-catalysis have also been used for such reactions, including flavins, Eosin Y and quinones due to their interaction with light.[17]

1.6.1.2.2 Oxidation

Oxidation reactions are some of the most important chemical reactions in chemistry and the introduction of the oxygen atom can sometimes be significantly difficult to achieve. This is often achieved with harsh chemicals, such as permanganates or super oxides. It is because of these highly dangerous chemicals that hydrogen peroxide is seen as a clean alternative in such reactions[18].

1.6.1.2.3 Reduction

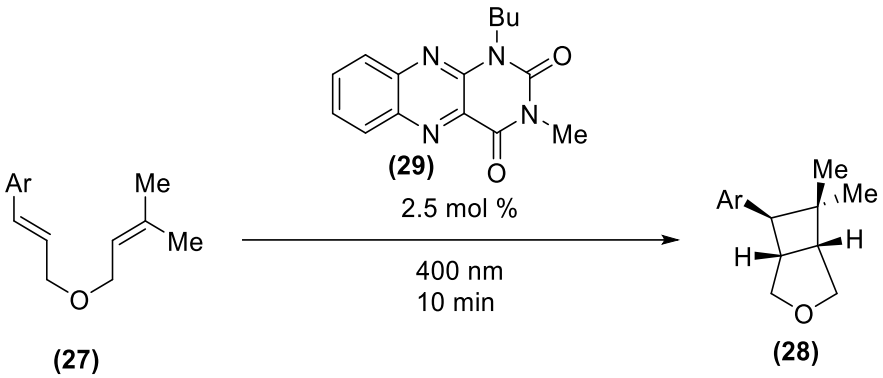
Photochemical radical reactions tend to be redox reactions meaning that so for any oxidation that takes place, something else has to be reduced. There are a number of oxidation reactions that have been studied in literature, with one such reaction being the reduction of nitro benznes to phenylamines.. An interesting fact about this reaction is that no hydrogen donor is added, and all hydrogens are extracted from the solvent, in this case ethanol (scheme 1.5)[19].



Scheme 6: Reduction of nitro benzene to aniline using eosin Y and light

1.6.1.2.4 [2 + 2] cycloaddition

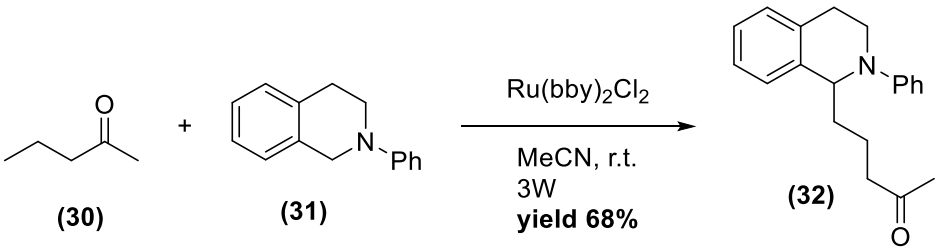
As discussed earlier a [2 + 2] cycloaddition is not allowed by traditional thermal techniques and the only way to have such reactions is to use photochemistry. This reaction can give rise to 4 membered rings that are highly important when it comes to active pharmaceutical reagents (Scheme 1.6)[20].



Scheme 7: Intramolecular [2 + 2} cycloaddition using photochemistry

1.6.1.2.5 Nucleophilic attack

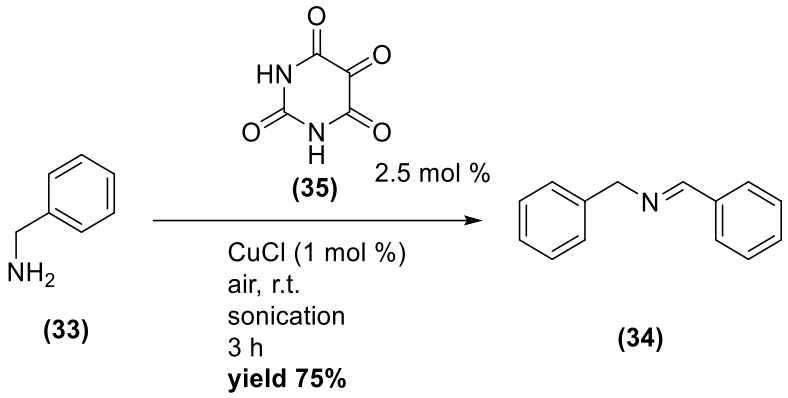
adding a nucleophile to a carbon-hydrogen bond tends to be challenging, normally requiring a number of expensive metal catalysts. Photochemistry offers a new route into the preparation of new carbon-carbon bonds with the simple use of a nucleophile and light (Scheme 1.7)[22].



Scheme 8: Nucleophilic attack to a tertiary amine using eosin Y and light

1.7 Imines

Some of the previous work that has been done in the Carbery group has focused on the oxidation of amines to imines using radical chemistry, including the use of a Copper/alloxan dual system that dehydrogenates benzyl amines into imines as seen in Scheme 9: amine dehydrogenation using a dual catalytic system of alloxan and copper. A similar reaction was also performed using a Flavin/alloxan dual system with dimethylsulfoxide as an electron donor, with the imine being the product. Any modification of these reaction to have a photocatalysed reaction would result in an imine formation and a brief understanding of imine chemistry can be seen below[23].



Scheme 9: amine dehydrogenation using a dual catalytic system of alloxan and copper.

Imines possess the general formula of $R_1R_2C=NR$, which means that a carbon is double bonded with a nitrogen which can then be itself bonded to an aryl, alkyl or a hydrogen. If the nitrogen is not attached to a hydrogen it can be named a Schiff base, which have a number of different uses as an anti-microbial and ligand for metal co-ordination.[24]

1.7.1 Imine preparation

There are a number of ways to prepare imines, especially when it comes to metal catalysis. An imine is the simple product of an aldehyde reaction with a primary amine, to form an alcohol amine which then loses water to form a carbon double bonded with a nitrogen[25].

An alternative synthetic route to imines is by oxidation of amines which does not require the aldehyde. This can be done using a number of different approaches including metal catalysis and radical initiation.

A number of reactions have been used throughout the years to make this process commercially viable and although this has been successful, the reactions are quite unsustainable, using

stoichiometric environmentally unfriendly reagents rather than catalysts, such as dichromate and permanganate ions, manganese and silver oxides and lead tetraacetate.

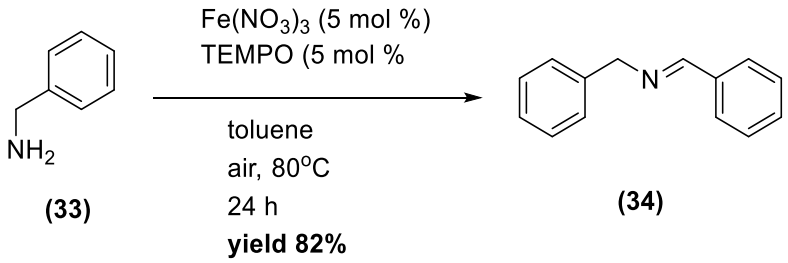
Since a number of different approaches have been used in order to try and make this process more sustainable and more economically viable, when one looks at literature, there are a number of reports suggesting different methods of how to synthesise imines, including, but not limited to;

- Reactions of alcohols/aldehydes with amines
- Oxidation of secondary amines to their corresponding imines
- The use of biomimetic/bioinspired catalysts such as flavins for amine oxidation

The ease with which aldehydes and amines react together to form the imine is noticeable, but the by-product of the reaction is water, which can then react with the imine to go back to the starting material. This would mean that the water would have to be removed, either with the use of a drying agent, or by boiling it off using a Dean Stark.

Although metal catalysis has advanced significantly, a number of metals are not as abundant on the earth's crust, and therefore their use must be limited if sustainability is to be reached.

One fo the cleanest approaches found in litereture is the use of Iron as a catalyst as described by Zhang[26]. A number of imines were prepared using dual catalysis made up of iron nitrate and TEMPO in toluene. The starting materials ranged from amines only, to amines with alcohols and amines with anilines, with most of the reactions giving a very good yield of over 70%.

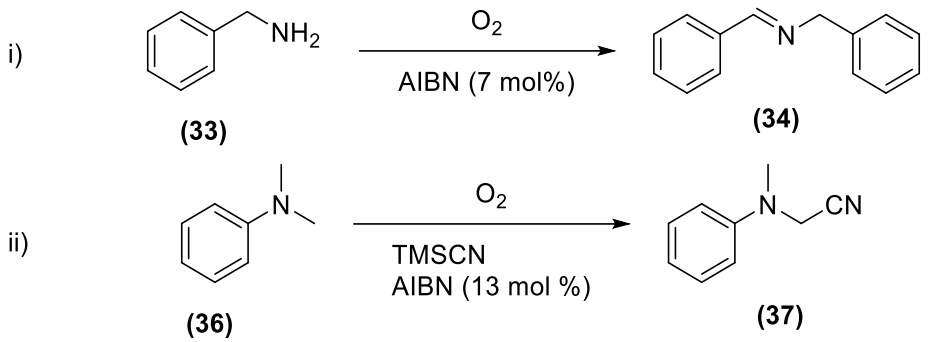


Scheme 10: One of the imines prepared by Zhang using iron salts as a catalyst.

1.7.1.1 Radical initiation

Imine formation can be easily initiated by using AIBN which is a radical initiator. The role of this initiator would be to introduce radicals which can then extract a hydrogen, transferring the radical onto the amine.

This type of mechanism can be used for both primary and secondary amines, giving different products in both cases (Scheme 1.9)[27].



Scheme 11: Radical initiation in the preparation of imines, i) oxidation of primary amine, ii) oxidation of secondary amine

Imines tend to be easily hydrolysed to amines and aldehydes in the presence of an acid. This route gives a simple way to change functionality from an amine to an aldehyde, introducing an oxygen in place of the nitrogen.

On the other hand, when a secondary amine produces an iminium ion, the nitrogen is positively charged, which makes this compound a very good electrophile. This can then react with nucleophiles which can introduce an additional functional group on the same molecule.

1.7.1.2 Metal catalysis

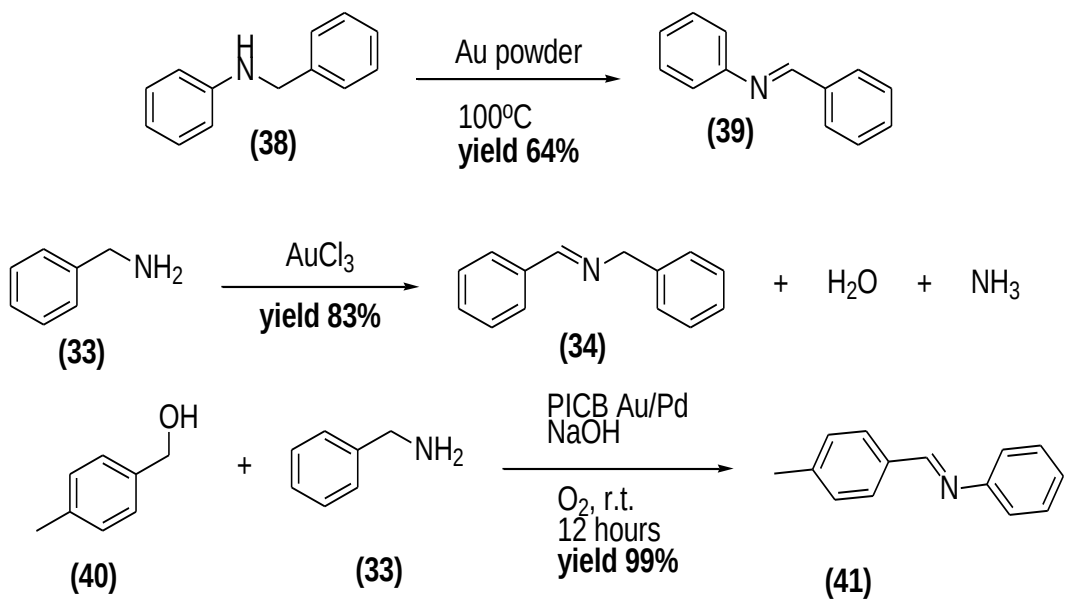
In chemistry, the use of catalysis is highly important, and a lot of money is spent in developing new catalysts with improved conversion and reaction times and reduced reaction temperature and reduced catalyst loading.

There are a number of different types of catalysts and these can be discussed using gold as an example of imine preparation. Scheme 12 shows a number of reactions with gold being the catalyst in different forms and shape;

- Homogenous, where all the components are at the same phase;
- Heterogeneous, where the catalyst is in a different phase to the reactant such as a solid catalyst with the reactants in solution and;
- bi-metallic systems where the catalyst is supported and activated by another metal.

When using expensive metals such as gold heterogeneous catalysts offer a distinct advantage. Since they can be easily recycled and reused. However it is common to use higher catalyst loading to get the same activity since the amount of gold that can be used in the reaction would

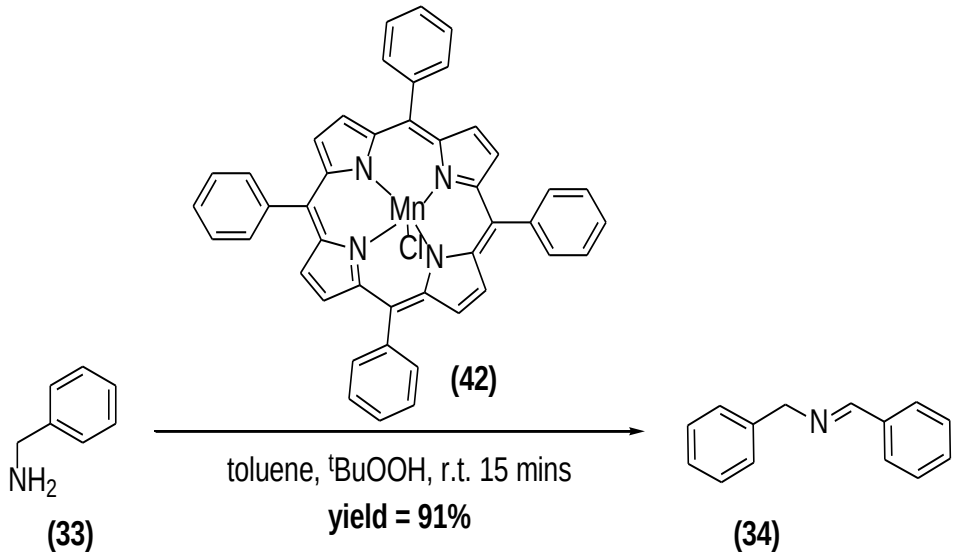
be the outer layer only, in contrast to every single molecule when the catalyst is in solution[10,28–30].



Scheme 12: Imine preparation using gold, i) gold as solid, ii) gold in solution, iii) bi-metallic gold

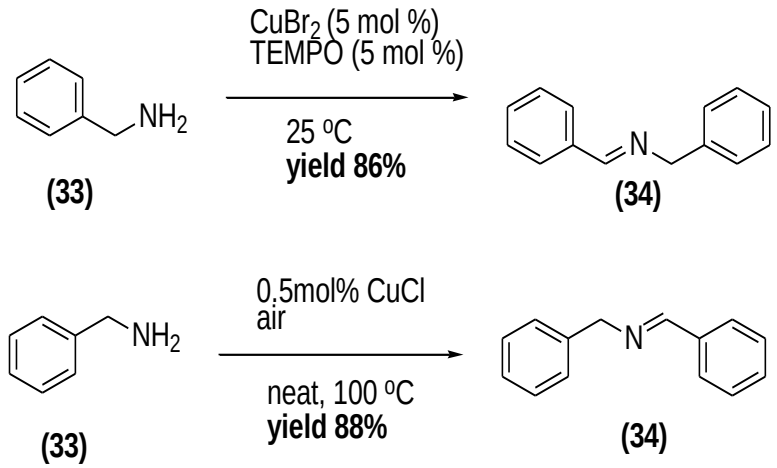
Considering that, gold is quite expensive other options were explored and both copper and manganese gave good results in the oxidation of amines.

Manganese oxidation is fast and occurs at room temperature, which is ideal for industry but it requires a better oxidising agent than oxygen in the air as seen in Scheme 1.5.[31].



Scheme 13: Oxidation of amines to imines using a manganese complex

Copper was the catalyst chosen for the imine preparation. One such reaction, which is solvent free, uses air as an oxidant and low catalyst loading (Scheme 16)[32–35].

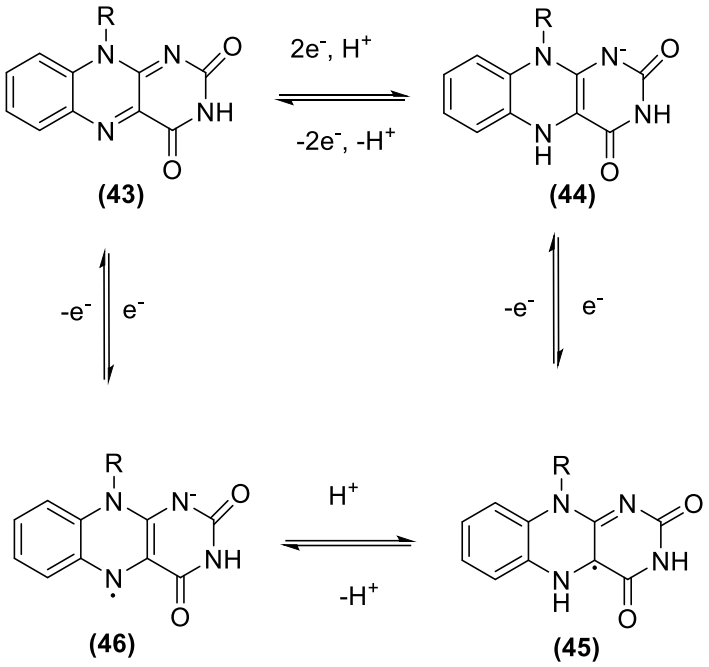


Scheme 14: Oxidation of amines to imines using copper as a catalyst

1.8 Flavin Chemistry

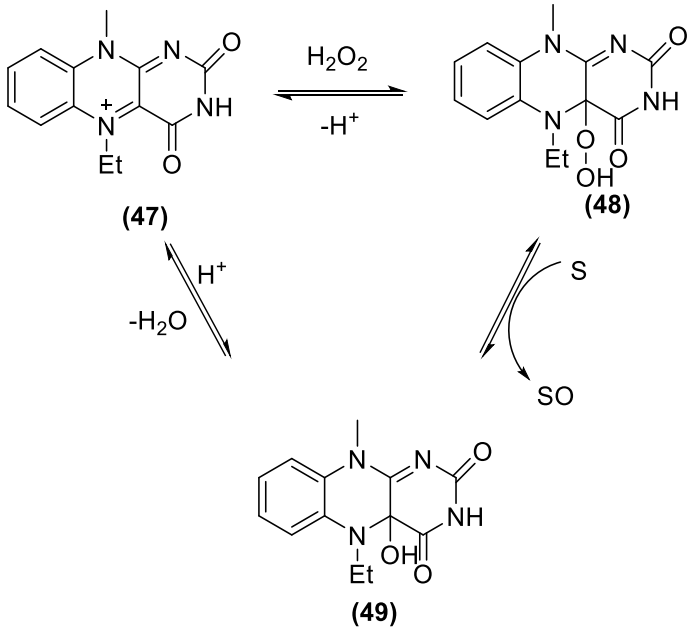
The use of visible light to catalytically mediate a redox reaction is of great interest. Using visible light for substrate activation allows for the preparation of a sustainable complex reaction with the use of mild conditions. Riboflavin is a biologically active molecule, capable of acting as an organocatalyst in non-light driven reactions but it is also possible to excite flavins using light. This use for flavins as photocatalysts has not been extensively researched when compared to its non-photochemical reactions[36,37].

The redox potential of flavins are depicted in Scheme 15. Flavins can undergo sequential electron uptake, yielding three different oxidation states. From the fully oxidised quinone **(43)** one electron uptake and protonation yields semiquinone **(44)**, that can take up another electron to yield the fully reduced hydroquinone **(45)**[38]**.**



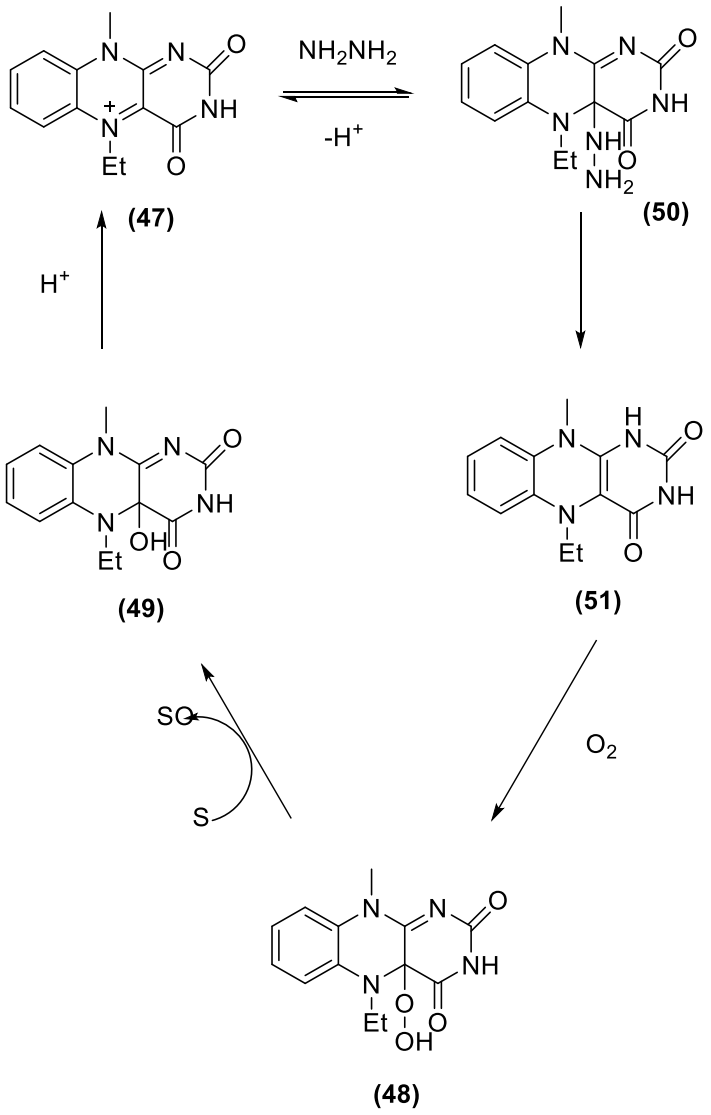
Scheme 15: Possible oxidation states of a flavin molecule.

Murahashi et al used 3N-methyl-5N-ethyl lumiflavin perchlorate salt **(47)** as a catalyst precursor in the anaerobic oxidation of tertiary amines to N-oxides, N-hydroxylamines and secondary amines to nitrones and sulfides to sulfoxides. The catalyst is then prepared in-situ with the addition of hydrogen peroxide and the flavin peroxide being proposed as the catalytically active species, resulting in the hydroxy flavin **(48)**. The catalyst is then regenerated using hydrogen peroxide, as seen in Scheme 16[39,40].



Scheme 16: The catalytic cycle of flavin in the oxidation of sulfides to sulfoxides.

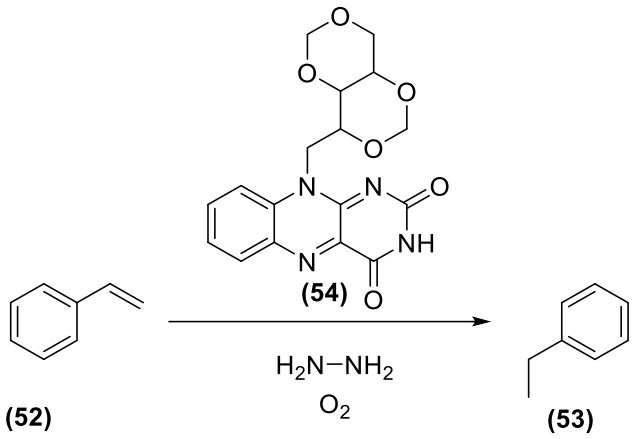
Hydrogen peroxide is a strong reagent and whilst the use of flavin as a catalyst is a step in the right direction in using more benign conditions Murahashi developed a micellar system where the oxidant was hydrazine, which is a much weaker oxidating agent than hydrogen peroxide. The main difference between the two reactions is that in this case, oxygen from the air would then replace the hydrazine-flavin molecule **(50)** which then creates molecule **(51)** and then continues the same reaction pathway as Scheme 16. Scheme 17 shows the catalytic cycle oxidation with a flavin[41].



Scheme 17: The catalytic cycle of flavin oxidation with the use of hydrazine

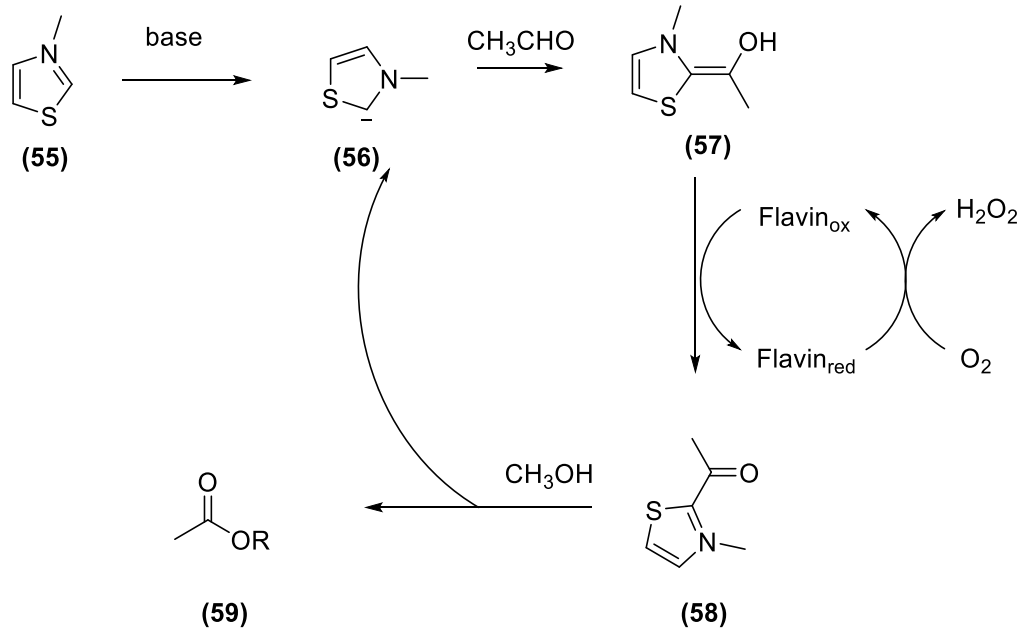
The principle of in situ generation of the diimide which is the primary catalyst of the reaction was also used in the organocatalysis of the reduction of alkenes into alkanes under aerobic conditions. The formed diimide is able to reduce alkenes with only nitrogen and water as the by-products which are two products that are chemically benign. Naota et al improved the

aerobic hydrogenation of alkenes by using an easily accessible neutral flavin as an organocatlayst. By extracting the reaction mixture with acetonitrile both the products and the catalyst were obtained, allowing for the reuse of the catalyst[42,43].



Scheme 18: Alkene hydrogenation using hydrazine and flavin

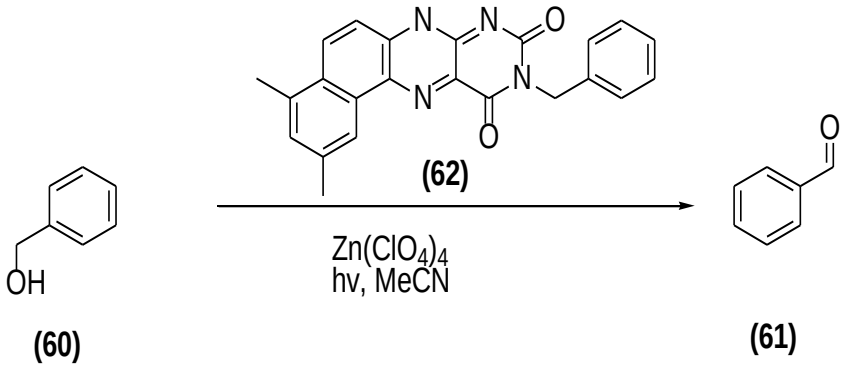
An interesting application of flavin catalysis was explored by Yano et al and Shinkai et al, who developed the flavin/thiazolum ion couple system for the oxidation of aldehydes into the corresponding esters. The proposed reaction mechanism can be seen in Scheme 19[44].



Scheme 19: A flavin/thiazolium ion couple system for the oxidation of aldehydes into the corresponding esters

Shinkai et al found out that upon co-ordination of the flavin with Zr^{4+} ion the oxidation power increased drastically, attributing this increase to the withdrawing properties of Zr^{4+} on the flavin molecule. They followed this discovery by exploiting this increase in oxidising potential to

remove oxidising agents such as hydrazine and H_2O_2 and induce the reaction using photo-excitation. The photo-induced reaction was able to not just oxidise benzyl alcohols, but also aliphatic alcohols, in contrast to the thermal oxidations[45].



Scheme 20: Oxidation of alcohol to aldehyde using photochemistry

1.9 Eosin Chemistry

Whilst flavins are naturally occurring, these are not the only organic based catalysts that are used for photoredox reactions. Another molecule that is being used in this area of chemistry is Eosin Y, which is normally used in histology, which is the study of microscopic structures or tissues.

The reason why Eosin Y is such a powerful tool in microscopy is because it is a highly colourful compound, absorbing light in the visible spectrum. This light absorption makes it an ideal candidate as a photocatalyst, with its absorption spectrum as seen in Figure 8.

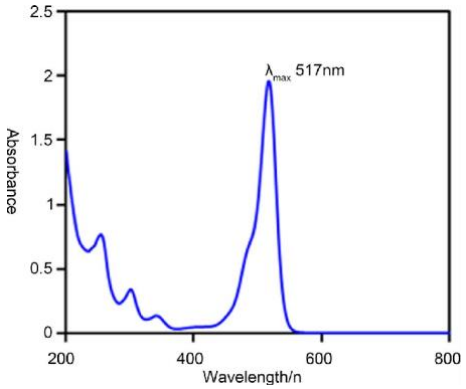
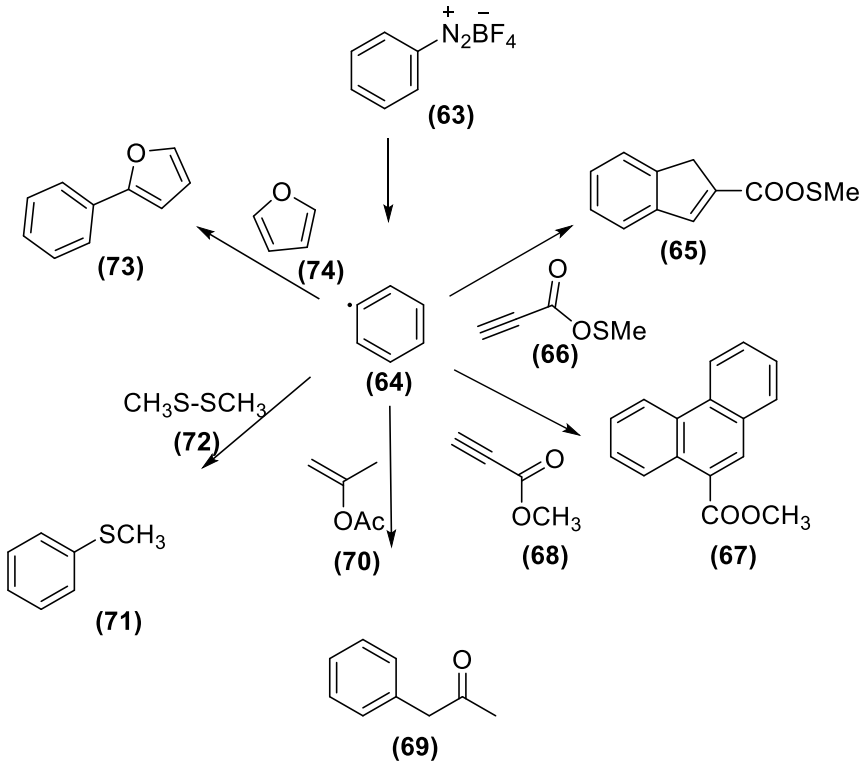


Figure 8: Excitation spectrum of Eosin Y in water

Two of the most researched reactions where Eosin Y is the photocatalyst are with tetrahydroisoquinolines and diazzonium salts, both of which give a number of very interesting and useful reactions.

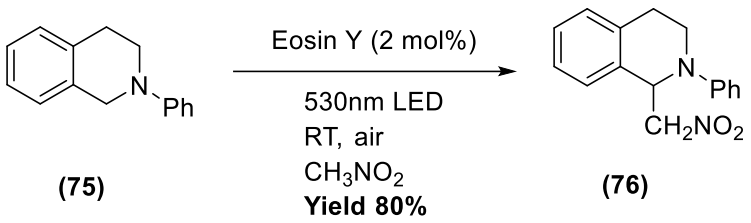
One of these reactions is the Phenanthrene Synthesis, a [4+2] Benzannulation of Biaryldiazonium Salts with Alkynes as seen in Scheme 21. This is an intramolecular reaction with the biaryl system laying the foundations for the formation of the phenanthrene, and the diazzonium salt proving as the ideal leaving group for the formation of a radical on the benzene ring[46].

Scheme 21 shows a number of other possible reactions that can be achieved through the removal of the diazzonium salt and preparation of the radical. The radical produces a very reactive site that can be easily attacked and forms new bonds that are very stable and difficult to reverse, producing a highly efficient way how to prepare complex molecules with simple reagents[13,47–50,51].



Scheme 21: A number of reactions that undergo radical addition.

In the previous set of reactions it was imperative that a leaving group was present in order to make produce the radical, as otherwise the reaction would simply not work. Eosin Y can also catalyse reactions on tetrahydroisoquinilines, where a benzylic radical is produced resulting in mediated coupling of sp3 Carbon-Hydrogen bonds in the absence of an external oxidant. In Scheme 22 it can be seen that nitroalkanes, dialkyl malonates, malononitrile and dialkly phophonates have all been used in creating new carbon-carbon or carbon-phosphorous bonds with high yields simply by irradiating with visible light[52].



Scheme 22: A nucleophilic addition of nitromethane to tetrahydroisoquinoline.

1.10 Project Aims

Sustainability

When it comes to sustainability there has to be a shift from metal to organo catalysis and from heat to light activated reactions. This project aims to replace metal catalysts in the imine preparation to an organic molecule such as the flavin while using light rather than heating.

The best case scenario would be if sunlight can actually be used to activate these reactions, but at this stage the research should focus on getting high conversion rates are high concentration rather than aim at absorbing sunlight which would be at a much lower power than any light available under laboratory conditions.

Aim

1. Investigate the use of flavins in light catalysed reactions

From previous works mentioned above it is well understood that an alloxan/co-catalsyt system can easily oxidise amines into imines. Apart from this it has also been reported that flavins can act as photo-organo-catalysts. In this project it was aimed to combine these two systems in order to oxidise amines with the use of natural occurring chemicals and light in order to increase the sustainability of such reaction. If the reaction does work a full optimisation will be performed in order to obtain the best yield for this reaction. This will look at a number of different catalyst that could possibly improve the yield of the reaction.

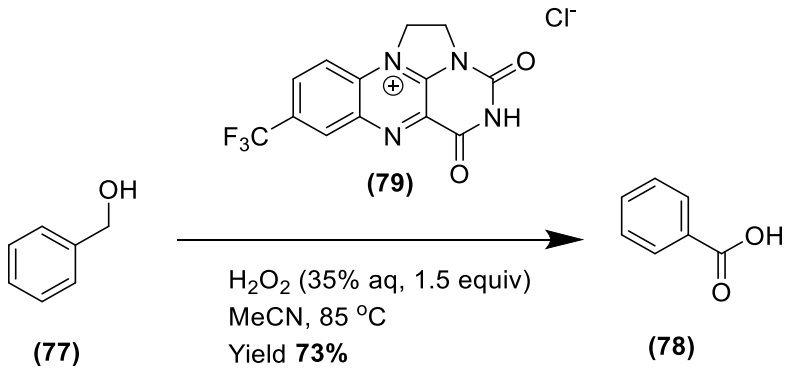
Chapter 2:
Amine Dehydrogenation

2.1 Introduction

Redox reactions using photochemistry have been used for a number of decades starting in the early 1900s[53]. Photocatalysts such as iridium and ruthenium complexes have been used so that when these absorb light and an electron is excited, forming an unpaired electron. This unpaired electron is a radical that can then be used to initiate a chemical reaction.

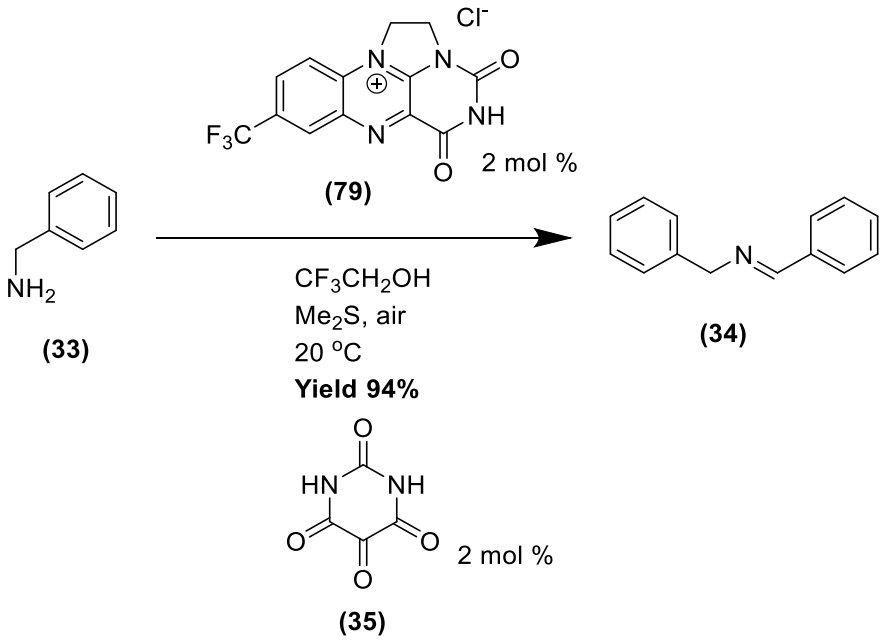
In previous works flavins have been used in conjunction with dimethylsulfide (DMS) to perform redox reactions without the use of light. DMS can interact with the flavin, donating an electron and initiating the redox reaction[54].

The first reaction that was analysed was the oxidation of alcohols to carboxylic acids Scheme 23 which resulted in very high yields of product, with the oxidant being hydrogen peroxide instead of oxygen.



Scheme 23: Oxidation of benzyl alcohol to carboxylic acids with the use of flavins and hydrogen peroxide

Another reaction which was studied was the oxidation of amines into imines, with the dimerization product being the only product of the reaction Scheme 24. These reactions were both very clean, with very little to no by-product being observed[55].

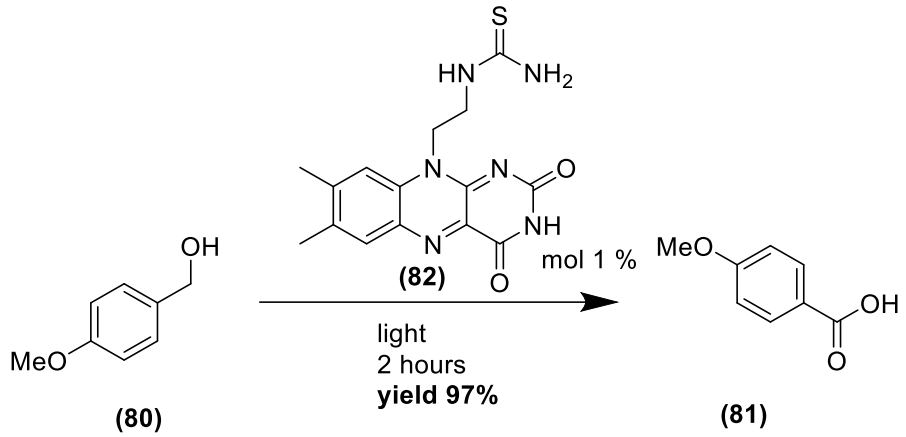


Scheme 24: Oxidation of amines to symmetrical imines using flavins and DMS

Murray had observed that flavins can easily accept electrons from DMS, and the immediate change in colour indicates that this reaction is instantaneous. Once flavins obtain this extra electron they become highly reactive, and thus these can be used in performing reactions that normally require some unsustainable strong oxidants, such as potassium permanganate for the oxidation of alcohols to carboxylic acids.

Amine oxidation to imines is another such reaction and whilst it is simple to create the imine from an aldehyde and an amine, there are few methods that can turn an amine into an imine if the aldehyde is not available. The use of flavins and DMS is an alternative route that can be used in the preparation of symmetrical imines.[55]

Whilst Murray was working on these oxidations, in Germany Konig and his team were working on a number of photochemical reactions, including the oxidation of alcohols to aldehydes as seen in Scheme 25[56].



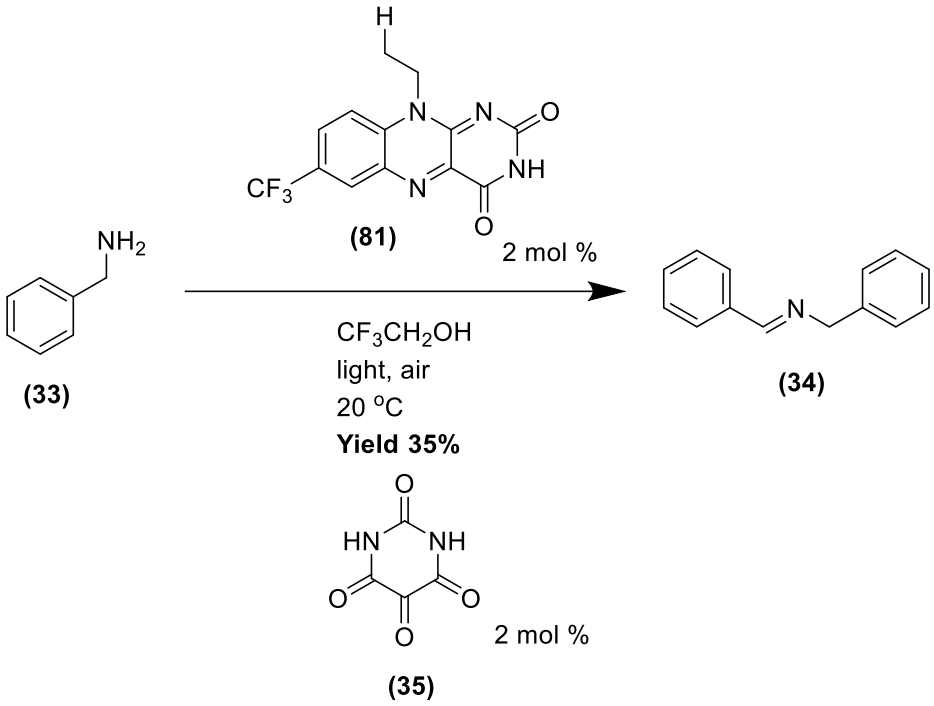
Scheme 25: Oxidation of methoxy benzyl alcohol with flavin photochemistry

The research by Murray and Lechner gave similar results, where alcohol was oxidized in both instances. This allowed for Murray's research to progress a step forward and eliminate the DMS, which ensured that these oxidations were more environmentally friendly. A comparison of the two sets of reactions can be seen in Table 1.[18,54]

	Murray	Lechner
Catalyst	Flavinium cation	Flavin
Solvent	TFE	Acetonitrile
Initiator	DMS	light
Product	Carboxylic Acid	Aldehyde
Yield	73 %	97 %

Table 1: Comparison between the reactions as performed by Murray and Lechner

After comparing these two reactions it was noted that for the oxidation of amines reaction the DMS could be removed for a light source, and other than that, the reaction scheme as performed by Murray could be used (Scheme 26)



Scheme 26: Exploratory reaction on the photo induced oxidation of amines to imines with flavins as a photocatalyst.

This first exploratory test reaction in this research resulted in a low conversion, with only 30% of the amine having reacted. Whilst the yield was low, this was encouraging as it showed that the reaction will work simply by removing DMS for light, turning the reaction into a photocatalytic reaction.

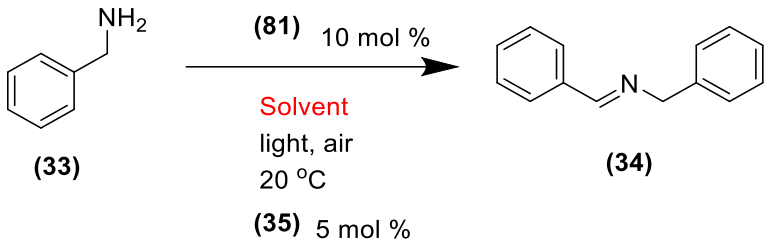
2.2 Solvent selection

In photochemistry, the solvent is very important, as it plays a key role in the stability of the radical. The more stable the radical is, the higher the possibility of having a successful reaction, and this increases the yield of the reaction.

In previous studies two of the most common solvents have been trifluoroethanol (TFE) and acetonitrile. Both of these solvents are polar, with TFE being a more polar solvent than acetonitrile, with the latter being a bit less polar than a normal alcohol. The fact that these solvents are polar is very important, as radicals are stabilized in polar environments. This preliminary knowledge was used to set-up a solvent screen.

Table 1 shows the solvents used together with the conversion of each reaction set-up. The first observation was that non-polar solvents were not as useful due to the fact that the alloxan and the flavin were only partially dissolving. This resulted in a lower conversion rate when

compared to the original reaction. Both TFE and acetonitrile gave similar conversions, and thus acetonitrile was used, being a more commonly available solvent.



Solvent	Conversion
Water	0%
Acetonitrile	37%
2,2,2-trifluoroethanol	35%
Ethanol	5%
Petroleum ether	0%
Hexane	0%

Table 2: Solvent screen for the reaction

DMF and DMSO were not used in this screening, mainly because these solvents are not environmentally friendly.All of the conversions were calculated using NMR spectra, with 0% conversion indicating that only the reactant's peaks were observed in teh spectra obtained.

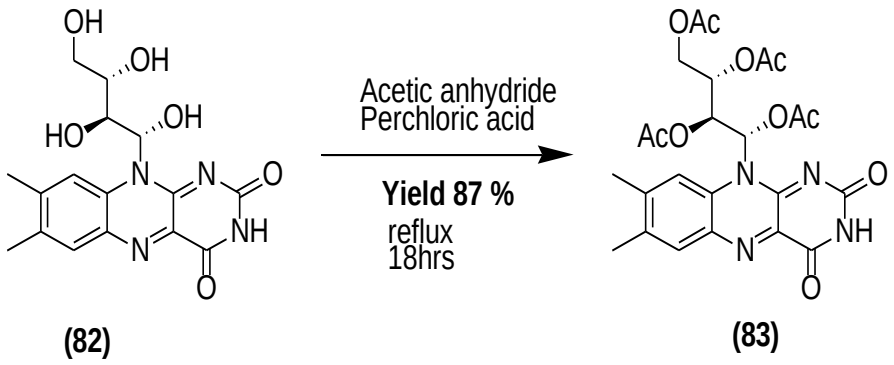
2.3 Catalyst selection

There are a number of different photocatalysts that can be used for this reaction and as such, a list of several catalysts was prepared. The most important aspect of such catalysts was the fact that all of these options were organocatalysts, meaning that only carbon, oxygen, hydrogen and in some instances, sulfur, were present in the molecule.

A number of flavin molecules were used in this study. The base structure of a flavin molecule is the pteridine and any different groups attached to this molecule can change the characteristic of the catalysts, such as its redox potential.

Riboflavin, molecule **(82)**, is a naturally occurring flavin, more commonly known as Vitamin B2. Its concentration in the human body is very low and thus this can dissolve and be transported in the blood. Under lab conditions, when riboflavin is used in the mg scales per mL, riboflavin is not as soluble and thus could not be used in these reactions. A way of increasing the solubility of a compound by introducing groups that can interact with the solvent

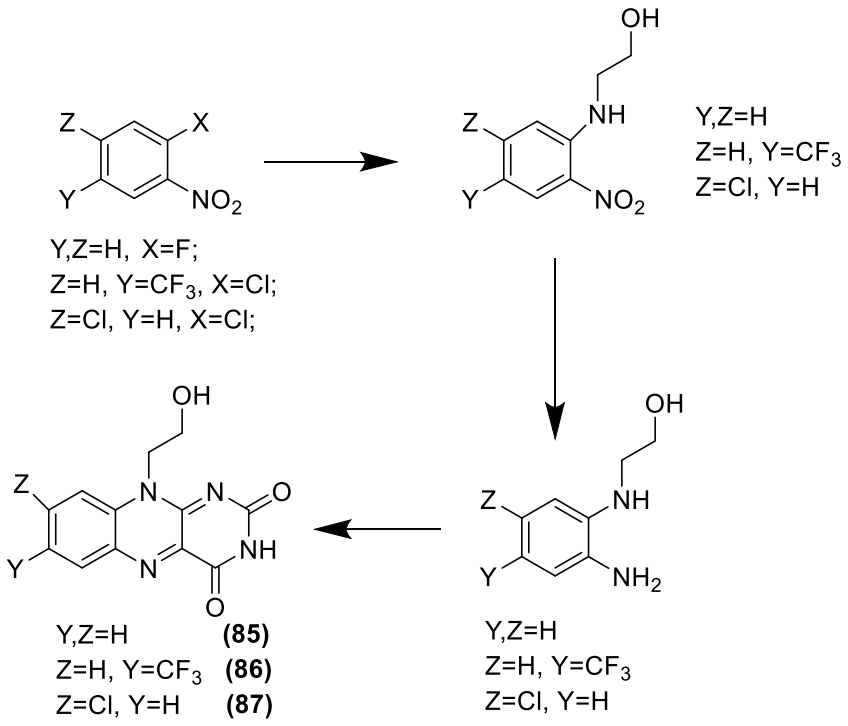
and in this case the group was the acetyl group. The ribityl sugar chain can be reacted with acetic anhydride and a few drops of perchloric acid as seen in Scheme 27.



(82) **(83)**

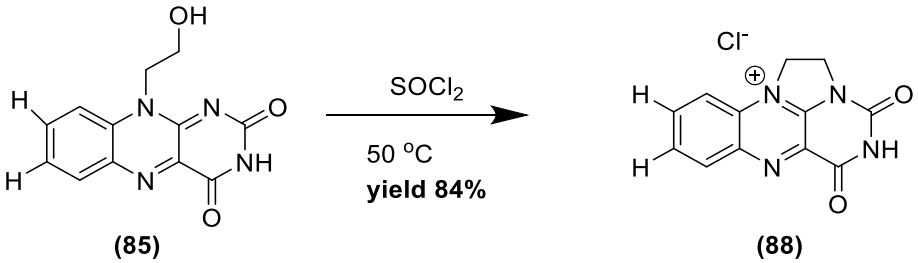
Scheme 27: Transformation of riboflavin into riboflavintetraacetate.

Riboflavin was not the only flavin that was used in the catalyst screening. A number of different flavin molecules were prepared; **(85)** to **(87)**. The preparation of such flavins follows a similar route, but the reaction scheme has to be adapted to each individual molecule as the side groups can end up taking part in different reactions. Scheme 28 shows a general reaction scheme for such preparations. The first step is an aromatic nucleophilic substitution of a halogen on an aromatic ring, however this reaction is not possible in the preparation of the Fluoro flavins as the ring would be too deactivated even with the nitro group activating the substitution. Once this nucleophilic substitution takes place a reduction of the nitro to the aniline is performed which would be a platform to react with alloxan and prepare the pteridine group. Once the nitro group is reduced, the product is slightly unstable, and the next step should performed immediately in the dark to make sure that the aniline does not oxidise back to the nitro group. These flavins were prepared in the Carbery group for the use of everyone in the lab.



Scheme 28: Preparation of the different flavin molecules

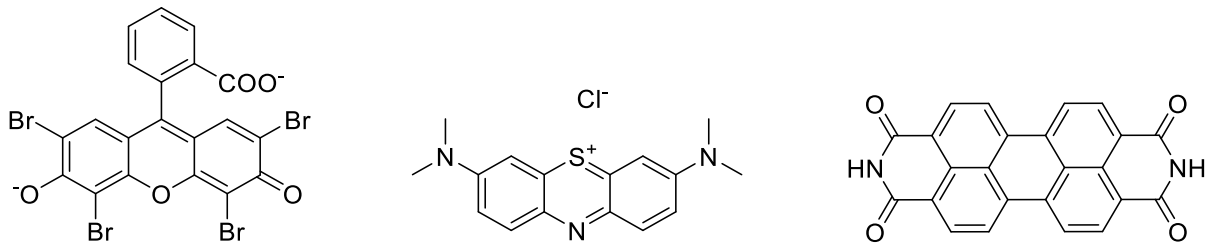
All of these flavins have the same basic structure, and the main difference between molecules is the functional groups on positions 3 and 4, with methyl groups, nitro and fluoro functionalities all offering a varying degree of electron withdrawing and donating group. These slight differences in electronegativity can stabilize or destabilizes the radical, making it a better or weaker oxidizer. Murray, during his research in the oxidation of amines to imines used cationic cyclic flavins, such as molecule **(88)** and this can be prepared from the previously prepared flavins by the addition of $SOCl_2$ as seen in Scheme 29.



Scheme 29: Preparation of the bridged flavinum salts by Murray[54]

The cationic flavins do not simply offer a completely different molecule with a positive charge that can play a huge role in the ring electron density, but it also shifts the electronic absorption spectrum to the left, from 450nm to around 400nm which is just in the visible range spectrum. This shift to the left limits the amount of light that can be absorbed from the light source used.

Flavins are not the only photo-organic-catalysts available and a number of dyes have also been used as seen in Figure 9. One of the most important things to realise from these molecules is that all of them have conjugation, which allows these structures to excite an electron from the HOMO to the LUMO by absorbing visible light. The fact that these molecules are coloured means that they absorb in the visible light region, but not all of these molecules will be good for a photoreaction because the excited electron should be similar in energy to the orbital of the molecule it needs to interact with.



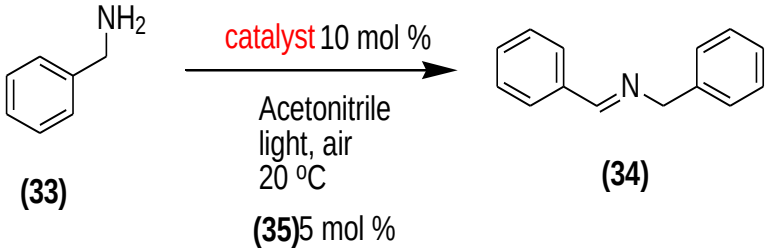
(89) **(90)** **(91)**

Figure 9: Three dyes that have been tested as photocatalysts; Eosin Y, methylene blue and a Perylene (from left to right)

Finding the right catalyst is very important in a reaction as this can result in a quick reaction time with high yields of product. That is the best scenario and thus for the catalyst screening both the reaction time and the yield of reaction were considered on their own merits.

Upon comparing the work done by Murray and Konig, it was immediately observed that in some instances a co-catalyst was used. This was also the case in a good number of reactions when an inorganic complex catalyst was used. With this reaction being based on what Murray had previously done, alloxan was used as a co-catalyst.

As can be seen in Table 3 the flavin molecules all worked as catalysts for this reaction, though none of these gave the same yields. The cationic flavin **(88)** gave a very poor yield, mainly due to the fact that its main absorption peak lies just at the edge of the visible light spectrum. The CF_3 flavin **(86)** and the unsubstituted flavin **(85)** gave a yield of just over 45%, which was quite satisfactory for this screening. Another molecule which also catalyzed the reaction with 40% was Eosin Y, but the other dyes **(90)** and **(91)** did not show any reactivity with the amines and no imines were produced.



Entry	Catalyst	Conversion / %
1	85	53
2	86	51
3	87	45
4	88 (cationic flavin)	12
5	89 (Eosin Y)	41
6	90 (Methylene Blue)	0
7	91 (Perylene)	0

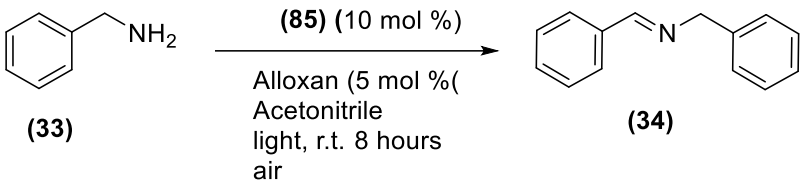
Table 3: Catalyst screening for the reaction.

From the screening it was noted that the H flavin **(85)** should be taken forward for optimization, with the CF_3 flavin **(86)** and Eosin Y **(89)** also being set aside if the reaction could not be optimized with the H flavin.

2.4 Ensuring Catalytic Conditions

In the catalyst and solvent screen, the reactions were set-up with 10% each of the catalyst and co-catalyst. The conversion rates obtained were higher than the catalyst loading, which indicated that the reaction is catalytic, with a very low turnover of only 4 to 5 times of the catalyst in each reaction. Before optimizing the reaction it was important to ensure that all of the variables taking part in the reaction are important for completion of the reaction.

The variables in this experiment can be seen in Table 4. A number of experiments were performed so that one variable was removed from each of the experiments in order to verify the necessity of each variable. The four variables in the reaction were; catalyst, co-catalyst, air and light. If the reaction does not occur when any of these variables is missing then that variable is vital for the completion of the reaction.



Air	Catalyst	Co-catalyst	Light	Yield / %
x				0
	X			0
		x		5
			x	<2
				53

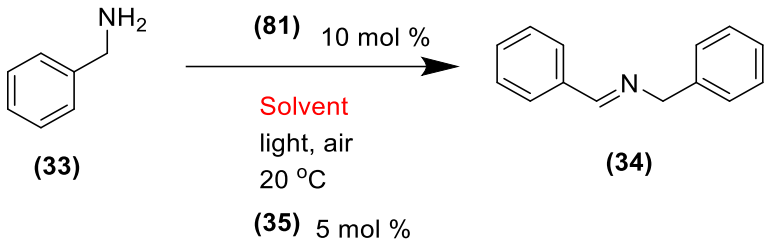
Table 4: Testing all the variables in the reaction

Table 4 indicates that the reaction only gives a reasonable yield when all of the variables (air, alloxan, flavin and light) are present. Very small amounts of reactivity could be observed through NMR analysis when no alloxan was used in the reaction. This low yield could indicate that the reaction can still take place without the alloxan, but longer reaction times have not changed the conversion for alloxan, indicating that this might be needed in the recyclability of the flavin. When no light was present there was a hint of a background reaction, with new small peaks being seen in the NMR in areas where the imine would be observed however longer reaction times showed that these peaks barely changed indicating that if any background reaction was present, this was very slow.

When the flavin was the variable that was left out of the reaction no reaction took place. This shows that the flavin is actually an active catalyst in the reaction that is needed to initiate the reaction, in contrast to the alloxan which is only needed to regenerate the flavin catalyst. This also showed that this reaction needs a dual catalyst, with one molecule interacting with the reactant, and the other turning over the catalyst. This is in line with what Murray had found when he noted that the two catalysts need each other for the reaction to proceed.

On analysing the reaction mixture with NMR, it was immediately discovered that there was a small but significant peak corresponding to benzaldehyde. This is the product of hydrolysis of the imine, where the aldehyde and the amine are given off. In a study prepared by Lechner[57] it was noted that the reaction always gave the aldehyde, except when completely dry conditions were used. This was not the case in this study as the aldehyde was only a minor product that did not increase if the reaction was left for longer. Another observation was that the addition

of water to try and induce this oxidation did not result in more aldehyde, but it did stop the reaction when the ratio of water to alcohol was changed to 10% as seen in Table 5.



Solvent	Yield%
Pure acetonitrile	53
Acetonitrile + few drops of water	48
Acetonitrile + 10% water	8
Acetonitrile + 50% water	0
Pure water	0

Table 5: The effect of water on the reaction conversion

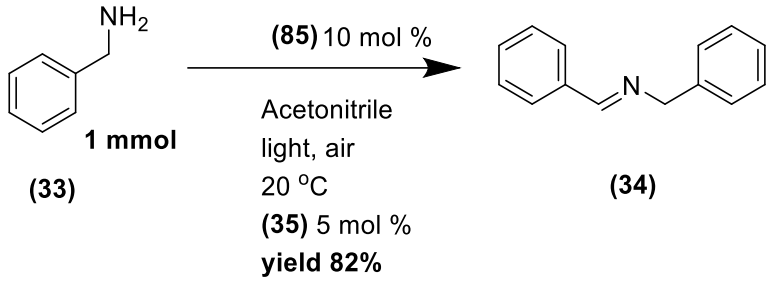
The reaction also needed air or specifically oxygen in this case in order to proceed, as this is the oxidant in this reaction. Without any oxygen no product was formed indicating that the catalyst on its own cannot oxidise the reaction of the amine to imine, though it is not known whether this oxygen is simply needed to turn over the catalyst or to interact with the amine itself.

2.5 Optimization

Upon concluding that all the variables were important and the best catalyst and solvent were found it was time for the optimization of the reaction. As this was an adaptation of the work done by Murray, the concentration might have been too high for a photochemical reaction. This ratio was very close to being 10:1 and this is very different from photochemical ratios found in literature where the concentration is in the 1mM scale or less[55]. This high concentration could end up quenching any radicals formed, thorugh the interaction of catalyst molecules together, and stopping the reaction from proceeding to completion.

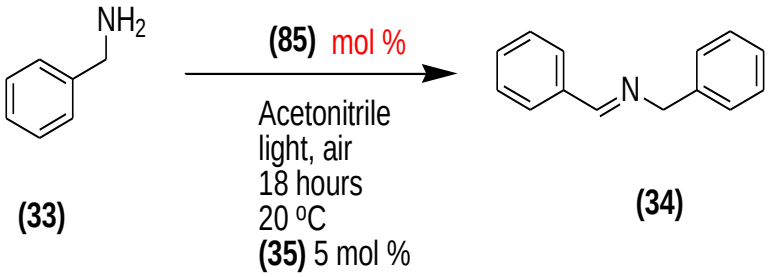
Such quenching could be caused by the concentration of either the catalyst or reactants. Two more set-ups were prepared, one with 1% catalyst loading in order to reduce the concentration

only and another with a 1mM solution of amine**,** with the catalyst loading remaining at 10% as shown in Scheme 30. The two reactions gave very different results, with the reduced catalyst loading only reaching 50% converstion and the reduced concentration giving a conversion rate of over 80%, with nearly no starting material being noted on analysis with NMR specetroscopy. This indicated that the reason why the reaction was stopping at 50% was because of the concentration.



Scheme 30: New reaction conditions after changing the concentration.

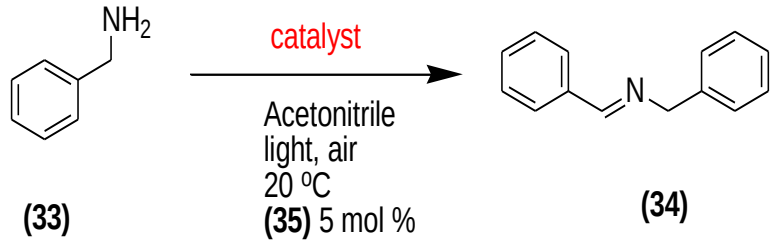
From the previous set of experiments it was also noted that the catalyst loading could possibly be reduced, mainly because when the catalyst loading was reduced to just 1% the reaction still proceeded to 50% conversion which was the limit under the used conditions. Table 6 shows the different catalysts loading that have been used together with the co-catalyst loading. It was deduced that 5% of each of the catalyst and co-catalyst was sufficient for the reaction to proceed to nearly 100% conversion without changing the 18-hour time-frame of the reaction.



Catalyst loading	Conversion / %
10%	82
5%	83
1%	50
0.1%	23

Table 6: Changing the catalyst loading

After analysing the results for the change in concentration and catalyst loadings it was observed that Eosin Y and H-flavin gave similar results in the catalyst screening and these had to be tested again to see if there was any difference in the reaction under these different catalyst. Table 7 lists the conversion of a number of reactions with the three different catalysts after 3 hours. The time of 3 hours was chosen as this would give enough time for the reaction to proceed, enabling the comparison of results and learning whether there was any effect when changing the catalyst. After 3 hours it was evident that Eosin Y was significantly faster and further testing showed that the reaction was complete after 8 hours.



Catalyst	Conversion / %
CH_3 flavin	74
Eosin Y 10%	97
Eosin Y 5%	96
Eosin Y 1%	97

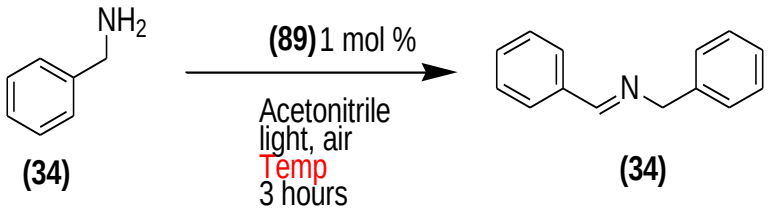
Table 7: Screening the reaction by comparison of the Flavin catalyst with Eosin Y

Temperature is a very important factor with regards to the speed of reactions. The Arrhenius equation, Equation 5 can be used to estimate the change in the speed of reaction when there is a change in temperature, with most reactions becoming twice as fast when the temperature increases by 10 ^{o}C.

$$k = Ae^{-\frac{E_a}{RT}}$$

Equation 5: the Arrhenius Equation

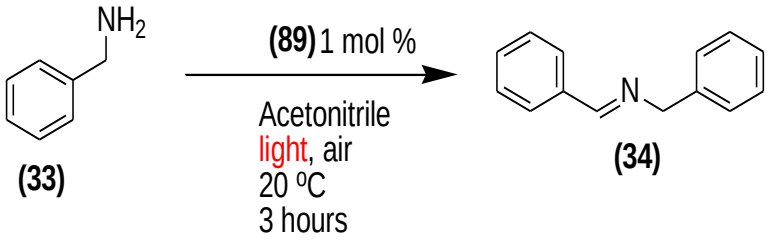
Table 8 shows the conversion of a number of reactions that have been prepared in different temperatures after 3 hours. As displayed in Table 8 there was no difference between the rate of reaction at room temperature and any of the other reactions that have been tested. Lower temperatures were also tested in order to ascertain whether this would have any effec on the overall conversion. These reactions also gave a similar conversion rate.



Temperature	Yield / %
90 ^{o}C	37
70 ^{o}C	35
50 ^{o}C	38
30 ^{o}C	40
0 ^{o}C	37

Table 8: Change of the rate of reaction on changing the temperature

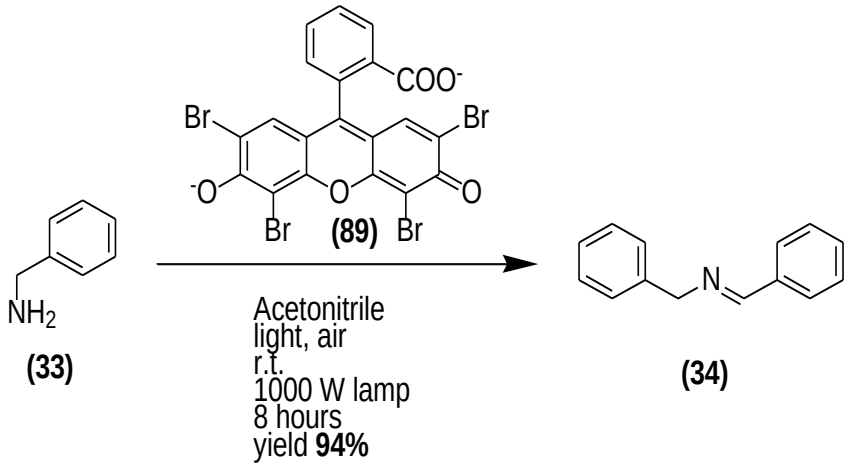
With all the variables in the reaction mixture being tested, the optimal conditions were found and the only variable that was left was the light source. All reactions were tested with a variable colour LED and thus the power of all the reactions was constant, using an LED lamp of 40W. When considering all the lighting options, different lamps were available, ranging from 5W to 1000W and these lamps were tried out in order to see if these would actually change the rate of reaction. Table 9 presents the results obtained by changing the light source after 3 hours, showing that the 1000W lamp white halogen lamp decreased the time to just 30 minutes. This implied that the limiting factor for this reaction was the light source. This indicated why there was no significant difference when the catalyst loading or temperature were changed.



Light Source	Yield %
1 Small LED	13
100 RBG LEDs	24
1 Large LED	46
1 spotlight	97
Lab light	0

Table 9: The effect of the light source on the reaction

As the light source was identified as a vital component, the reaction concentration was increased once more by a factor of 10 and whilst the reaction did go to completion, this took 10 times as long, indicating that the current reaction conditions were close to optimal. The optimal reaction conditions were set up as seen in Scheme 31.



Scheme 31: The optimised reaction conditions

Whilst the optimal reaction with respect to the light source was the 1000W halogen lamp this was heating up the reaction substantially. Even when cooling the reaction, the reaction time could not exceed 40 minutes and whilst this is just over the 30 minutes needed for the reaction to go to completion most of this research was done using the LED lamps, as these gave the same product under much safer conditions.

2.6 Substrate Screen

Once the reaction was optimized it was time to screen a number of different substrates in order to be able to assess the scope of this reaction. A number of benzylic amines were oxidised as seen in **Table 10.**

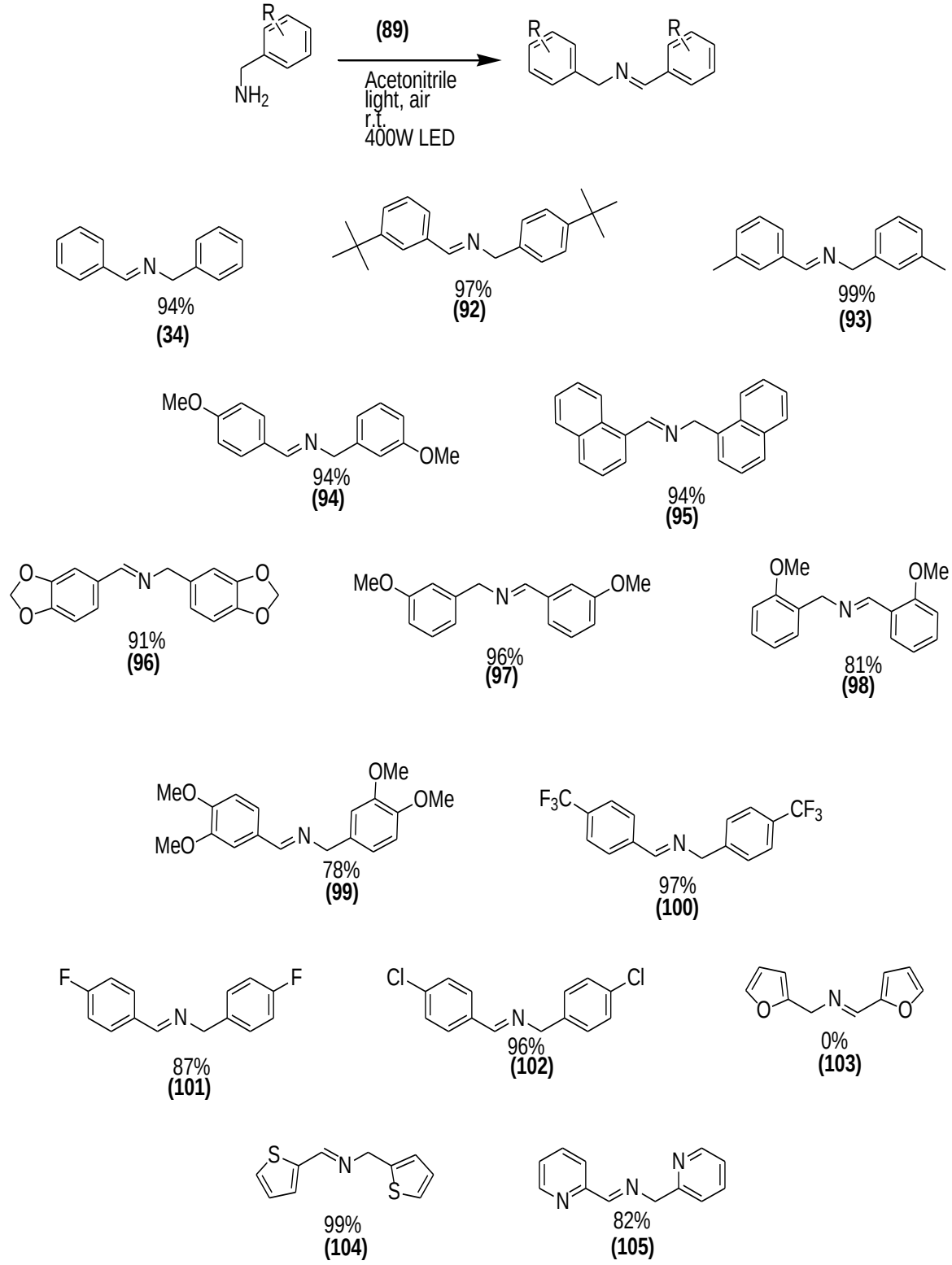
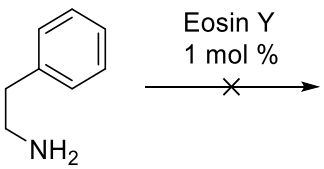


Table 10: Scope of the Eosin Y photocatalysed amine dehydrogenation

The reaction was generally efficient for most benzylic amines, with the exception of 2-furyl amine **(103)**, and 2,3-dimethoxylbenzyl amine **(99)**, which were incomplete after an extended reaction time, even when increasing the catalyst loading. 2,3-dimethylbenzyl amine was a slow reaction that plateaued after 65% conversion, which indicates that probably the product was hindering the reaction to progress further. The furfuryl amine was not producing the imine, with a white insoluble powder being produced and no starting material being present after 8 hours. When this reaction was stopped and analysed after 2 hours to analyse the reaction mixture and note if there was any imine produced after 2 hours, it was found that whilst not all the starting material was consumed there was still no sign of the imine dimer in the reaction mixture. The white powder was insoluble in methanol, acetonitrile and acetone and thus it was not analysed through NMR. Thiophenemethylamine, entry (**104**), also reacted to form the imine, even though that 5-membered rings are known to be resistant to oxidation when using transition metal mediated methods[58]. Electron rich substrates were particularly readily oxidised, and in contrast to what Murray had found in his studies, these were not oxidized further when the reaction time was extended, which he had found to be via further oxidation rather than hydrolysis[42,43,59].

In previous studies it was noted that aliphatic amines do not give the imine, with Murray even going on to say that the amine was actually inhibiting the reaction. In this study it was noted that when 100mg of octylamine were put in the reaction flask less than 20mg of chemical where recovered when the solvent was evaporated and the mass of the catalyst was deducted. This indicated that whilst it is unlikely that octylamine would evaporate due to its high boiling point, the products could still not be confirmed. When phenyletylamine **(106)** was tested out this again gave inconclusive results, and whilst the initial NMR showed an peak at the region of where the imine would have been present there were a number of smaller peaks throughout the spectrum and no imine was collected when a column was prepared.

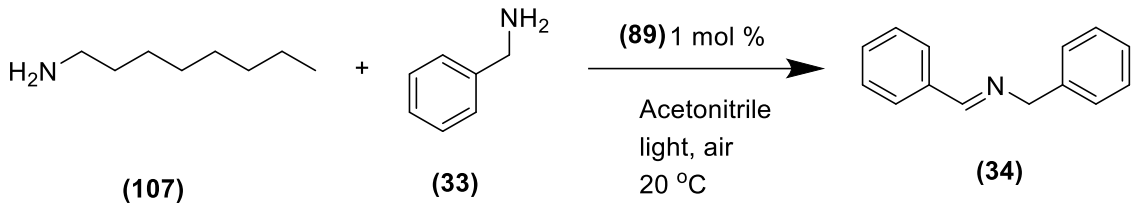


(106)

Scheme 32: The oxidation of phenethylamine

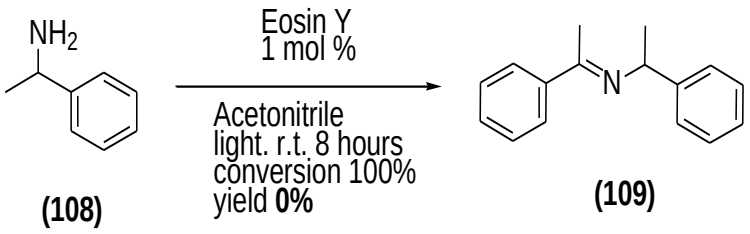
Murray's claim that the aliphatic amine was inhibiting the reaction was tested by oxidizing benzylamine in the presence of octylamine as seen in Scheme 35. In this reaction there was

complete conversion of benzylamine even with the presence of the octylamine in the reaction mixture, indicating that this was not inhibiting the reaction.



Scheme 33: Oxidation of benzylamine in the presence of octylamine

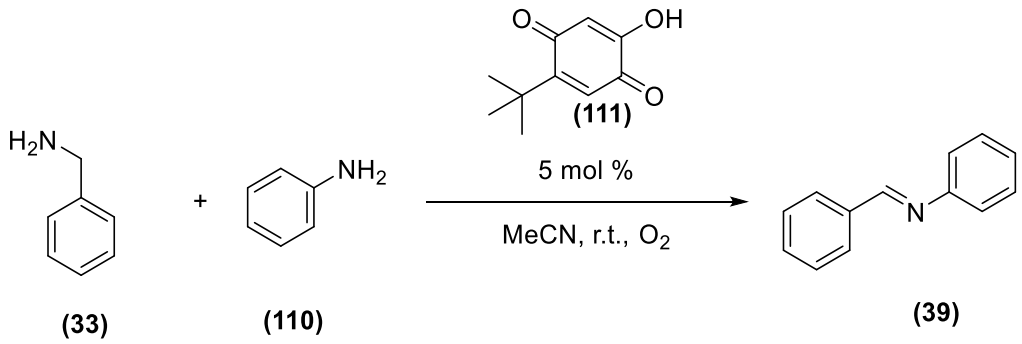
When alpha-methylbenzylamine was used for the reaction it was noted that a mixture of two products were formed, with this being possible the two diastereomers of the reaction. Again, this contrasts with what Murray had found where he noted that the alpha-methylbenzylamines were poor substrates for this reaction. The two diastereomers could not be separated into the individual components.



Scheme 34: Oxidation of alpha-methylbenzene.

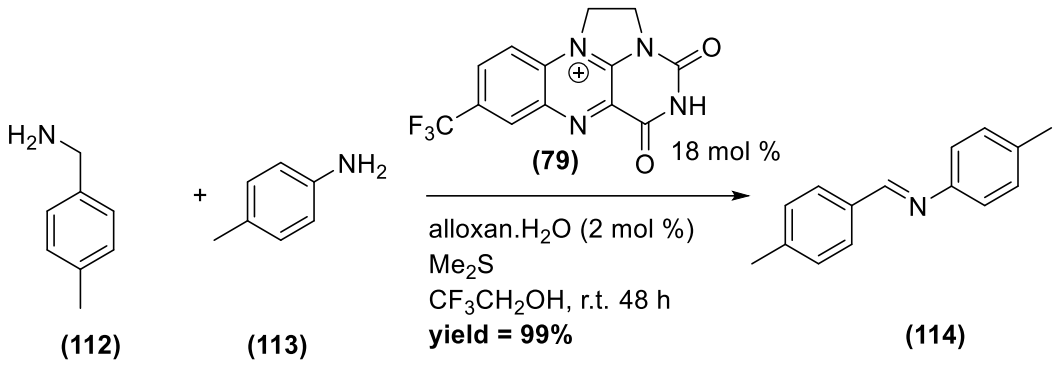
2.7 Amine Oxidative Cross Coupling

A number of recent publications which describe oxidations using quinone catalysts have shown that in some cases, cross coupling of amines to imines is possible[60].



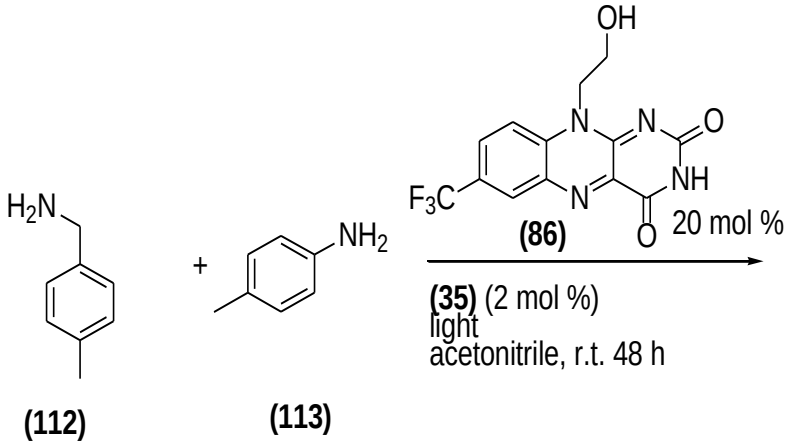
Scheme 35: An example of a cross coupling reaction. Ref

Exploratory attempts performed by Murray resulted in the main product being the cross coupling compound (**39**), with a massive improvement in selectivity by reducing the co-catalyst loading as seen in Scheme 36.



Scheme 36: A cross coupling reaction as performed by Murray

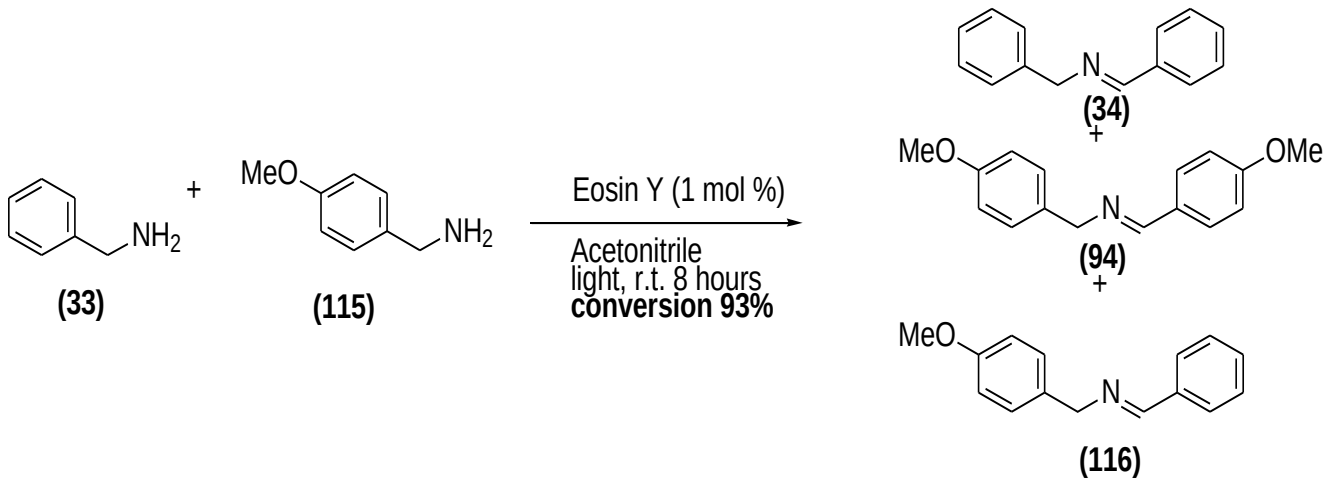
When some of these reactions were tested out it was noted that the reaction did not just not give the cross coupling product but the homocoupled product was also not obtained, with the catalyst being bleached turning from red to colourless. When this reaction was repeated with flavin no bleaching occurred though no oxidation products were obtained.



Scheme 37: An attempted photocatalysed cross coupling reaction

This reaction was then tried by adding the aniline 1 hour after the reaction was started and as soon as the aniline was added the reaction stopped. The reaction was being monitored using NMR spectroscopt. The fact that no more imine was produced after the addition of the aniline indicates that the aniline itself was interfering with the reaction. This cross coupling reaction did not result in any of the aniline reacting with the benzylamine.

Another cross coupling reaction that was analysed was the cross coupling reaction between different benzylamines as can be seen in Scheme 38. The results showed that whilst cross coupling does occur there was no preference to one product over the other, with a mixture being produced.

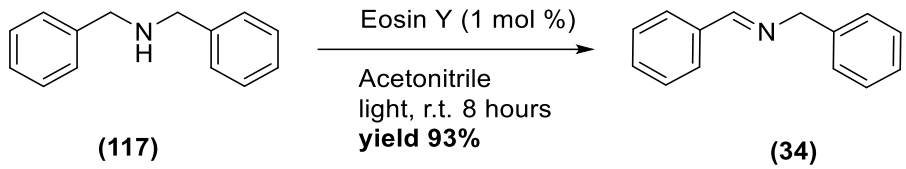


Scheme 38: Cross coupling reaction between to benzylamines.

When comparing the NMR spectra obtained with that of the pure imine products only 3 products were noted. Whilst this was very interesting no further work was done on the cross coupling of amines.

2.7 Secondary Amines

When looking at literature it was immediately noted that when oxidation of amines is discussed only primary amines are used, with secondary amines being described as unreactive or else with very low yields being produced. With the success of the primary amines oxidations it was thought that it would be possible to oxidise secondary amines into imines as seen in Scheme 39.



Scheme 39: A trial reaction to check the reactivity of secondary amines

The initial reaction was that on dibenzylamine, and it was immediately noted that this reaction gave complete conversion after 8 hours, indicating that it was possible to oxidise secondary amines. As can be seen from Figure 10 all secondary amines tested were oxidised to the imines with a high yield. One thing to note was that whilst in primary amines there were occasions where benzaldehyde indicating over oxidation, this was not the case for any secondary amines tested.

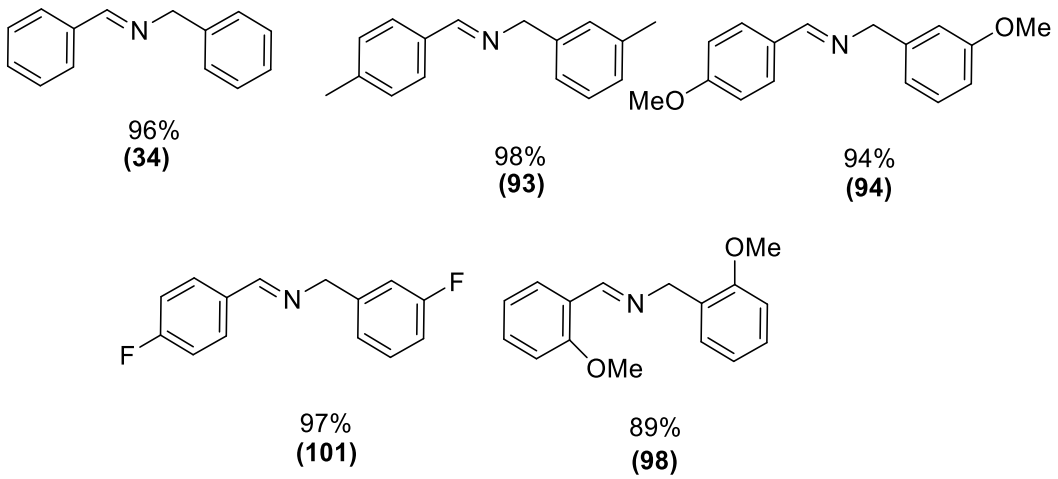


Figure 10: A number of secondary amines being oxidised to imines.

For dibenzylamine more Eosin had to be added as after 3 hours the Eosin had been bleached and the reaction could not proceed. On analysis of a sample from this reaction it was noted that the reaction had started, and thus more eosin was added, increasing the catalyst loading from 1% to 3%.

Once it was noted that secondary amines were being oxidised another question came up. Would unsymmetrical secondary amines have a preference to one side or the other? In order to assess this question a number of unsymmetrical amines were prepared. These included electron withdrawing groups and electron donating groups, in order to be able to evaluate the effects of the electron density on the ring on the imine formation. As can be seen on Figure 11 there was no preference to any one side of the amine, with the ratio being even in all of the unsymmetrical imines formed. This shows that once the radical is produced there is a resonance between the two aromatic groups, as otherwise there would be a higher proportion of the imine attached to the most electron donating para-substituted ring.

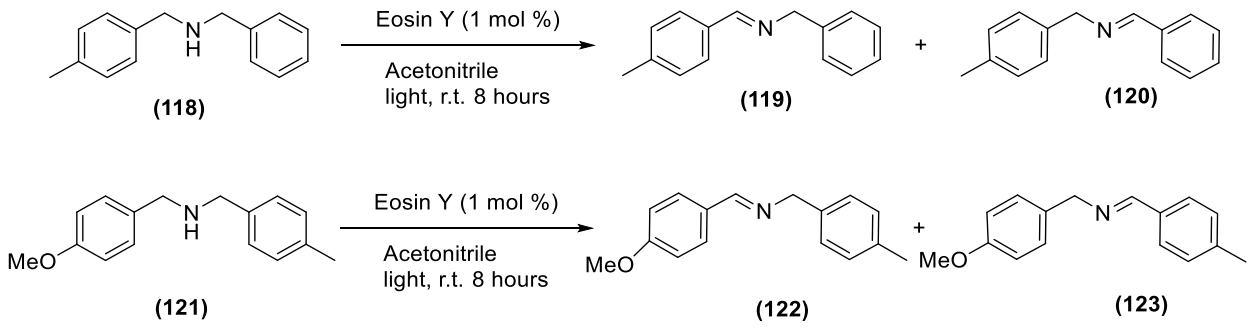


Figure 11: Oxidation of unsymmetrical secondary amines.

The reactions seen in Figure 13 were the only two reactions of the type done in this investigation. The NMR spectra obtained were compared with the pure spectra for the two different imines with the conversion for each imine being roughly equal. This was not studied further.

2.8 Greenhouse Reactions

Having an optimised reaction that works on both primary and secondary amines it was now time to test whether this system could work in direct sunlight. When the reactions were setup in the greenhouse the weather conditions were noted as with the temperature of the greenhouse. The reactions were than analysed to see how the reaction fare in direct sunlight.

Figure 12: Greenhouse chemistry, showing the greenhouse on the left and the beakers used on the right

When analysing the results, it was immediately obvious that the reactions do work in sunlight, but as can be seen in Table 11, repeatability was an issue. The reaction time was as fast as 20 minutes and as slow as 100 minutes, with the latter reaction being set up on a cloudy day, showing that even on the worst of days there was enough light energy to initiate the reaction.

Entry	Temperature / ^{o}C	Weather conditions	Time / min
1	45	Sunny with very few clouds	30
2	32	Cloudy with sporadic rain	80
3	47	Sunny with no clouds	20
4	36	Started sunny but soon afterwards clouds appeared and stayed visible for the duration of the reaction.	100

Table 11: A set of reactions that have been performed under sunlight in a greenhouse

One of the issues that was encountered in these reactions was the fact that the weather conditions were changing all the time, and thus there was no possibility of actually ensuring

two reactions were performed under the same conditions. This meant that for repeatability issues all the reactions were set up in the lab as this ensures that the weather conditions did not influence the reaction itself.

Chapter 3
Conclusions And Future Work

3.1 Conclusions

During this project the photo-catalysed dehydorgenative coupling of amines was studied and optimised. This was a very clean reaction, with only one product and very high yields.

Attempts to try and couple different amines together did not result in a single product, a reaction that was not studied further. A second coupling reaction between amines and anilines was also noted but no products were obtained for this reaction.

3.2 Further Work

Photocatalysis is an area of chemistry that is rapidly growing, and thus there is room for a lot of advancements in the area. As can be seen from this study organo catalysts can be used for photo—redox reactions, with the yields varying from low to very high.

The future of catalysis is very possible in flow chemistry. The main difference between flow and batch chemistry is that ina flow reaction the product is obtained continuosly. The main advantage of this system is that the catalyst can be reused as it would be implanted on the base of the reactor, whilst in a batch system it is very difficult to extract the catalyst, especially the flavin molecules as these tend to stick to the silica during column purification.

Chapter 4
Experimental

4.1 Materials and Methods

4.1.1 Chemicals

All reagents were purchased from either Sigma Aldrich, Fischer Scientifique and Fluorochem and used without any further purification.

4.1.2 Analysis and Purification

^{1}H NMR and ^{13}C NMR were performed on Bruker Advance 300 MHz.

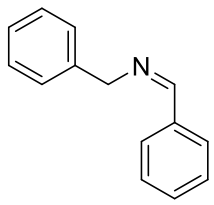
Mass spectra were obtained using an electrospray time of flight MicroTOF mass spectrometer. Samples were dissolved in HPLC grade acetonitrile or methanol and spectra were obtained using positive ionisation channels.

Large scale columns wer performed using Revelris Prep flash chromatography machine.

4.2 General Procedure for eosin catalysed photo-oxidative dimerisation of aromatic amines (General Procedure A)

The amine (0.1 mmol) was added to a solution of Eosin Y (0.01 mmol) in 100 mL of acetornitrile at room temperature. The resulting mixture was irradiated with green light. The solution was left open to air for 18 hours at room temperature, which varied from 15 ^{o}C to 25 ^{o}C. After the reaction, solvent was removed in *vacuo* and the remaining mixture was purified by passing it through a pad of base washed silica (2:1 petrol : EtOAc + 2% Et_3N) to afford the desired product

***N*-benzylidene-1-phenylmethanamine**



(34)

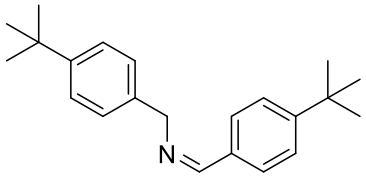
Following General Procedure A using benzylamine **(33)** (105 µL) for 10 h gave N-benzylidene-1-phenylmethanamine **(34)** as a yellow oil (95 mg, 94%).

^{1}H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.42 (s, 1H), 7.783-7.74 (m, 2H), 7.50 – 7.23 (m 2H), 4.75 (s, 2H);

^{13}C-NMR: (75 MHz) ($CDCl_3$) δ_C= 161.9, 139.3, 136.2, 130.7, 128.6, 128.3, 127.9, 127.1,65.00

Data in accordance with that previously published[55].

N-(4-(tert-butyl)benzylidene)-1-(4-(tert-butyl)phenyl)methanamine



(92)

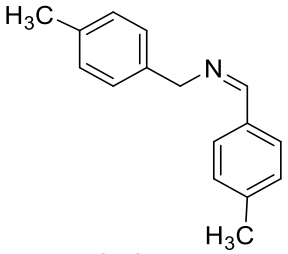
Following General Procedure A using 4-*tert*butylbenzylamine (120 µL) for 10 h gave N-(4-(tert-butyl)benzylidene)-1-(4-(tert-butyl)phenyl)methanamine **(92)** as a white solid (110 mg, 97%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.32(s, 1H), 7.72 (d, 2H, J=8.7), 7.46 – 7.15 (m, 6H), 4.62 (s, 2H), 1.25 (s, 9H), 1.23 (s, 9H).

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161.7, 154.2, 149.7, 136.4, 133.8, 128.0, 127.5, 125.7, 125.4, 65.1, 35.1, 34.5, 31.4, 31.1

Data in accordance with that previously published[55].

N-(4-methylbenzylidene)-1-(p-tolyl)methanamine



(93)

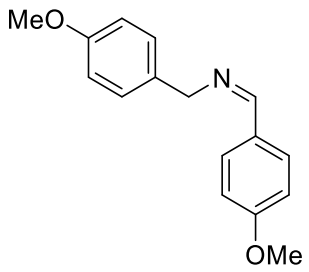
Following General Procedure A using 4-methylbenzylamine (105 µL) for 10 h gave N-(4-methylbenzylidene)-1-(p-tolyl)methanamine **(93)** as a white solid (99 mg, 99%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.41 (s, 1H), 7.63 (d, 2H, J=8.1), 7.19-7.01 (m, 6H), 4.67 (s, 2H), 2.34 (s, 3H), 2.30 (s, 3H)

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161.9, 139.3, 136.2, 130.7, 128.6, 128.3, 127.9, 127.1, 65.00, 36.2, 36.0

Data in accordance with that previously published[55].

N-(4-methoxybenzylidene)-1-(4-methoxyphenyl)methanamine



(94)

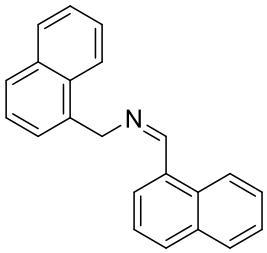
Following General Procedure A using 4-methocybenzylamine (100 µL) for 10 h gave N-(4-methoxybenzylidene)-1-(4-methoxyphenyl)methanamine **(94)** as a yellow oil (92 mg, 94%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.18 (s, 1H), 7.60 (d, 2H, J=8.6), 7.16 (d, 2H, J=8.6), 6.86-6.75 (m, 4H), 4.63 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H).

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161. 6, 161.0, 158.6, 131.5, 139.8, 129.0, 128.9, 114.1, 113.7, 64.3, 55.3, 55.1

Data in accordance with that previously published[55].

1-(naphthalen-1-yl)-N-(naphthalen-1-ylmethylene)methanamine



(95)

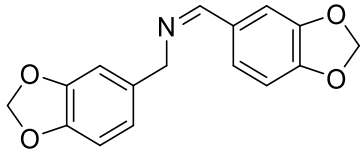
Following General Procedure A using naphtylmethylamine (150 µL) for 18 h gave 1-(naphthalen-1-yl)-N-(naphthalen-1-ylmethylene)methanamine **(95)** as a white solid (135 mg, 94%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.42 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7,.63 (d, 1H, J = 8.0 Hz), 7.51 – 7.27 (m, 5H), 7.21 – 7.02 (m, 7H), 4.82 (s, 2H).

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 162.0, 135.4, 134.0, 133.7, 131.7, 131.6, 131.4, 131.3, 129.3, 128.8, 128.7, 127.9, 127.5, 126.3, 126.1, 126.0, 125.6, 125.5, 125.4, 124.3, 124.1, 63.4.

Data in accordance with that previously published[55].

(Z)-1-(benzo[d][1,3]dioxol-5-yl)-N-(benzo[d][1,3]dioxol-5-ylmethyl)methanimine



(96)

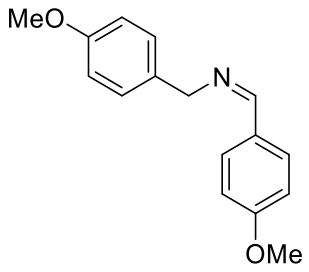
Following General Procedure A using piperonylamine (120 µL) for 36 h gave (Z)-1-(benzo[d][1,3]dioxol-5-yl)-N-(benzo[d][1,3]dioxol-5-ylmethyl)methanimine **(96)** as a white solid (101 mg, 91%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.23 (1H, s), 7.35 (s, 1H), 7.15 (d, 1H, J = 8.8 Hz), 6.81 – 6.63 (m, 4H), 6.01 (s, 2H), 4.65 (s, 2H)

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 163.9, 158.9, 157.9, 135.1, 135.0, 127.4, 126.1, 121.1, 118.4, 117.1, 113.2, 111.7, 111.5, 71.8, 64.3, 63.1

Data in accordance with that previously published[55].

N-(4-methoxybenzylidene)-1-(4-methoxyphenyl)methanamine



(94)

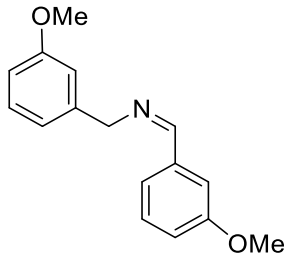
Following General Procedure A using 4-methocybenzylamine (100 µL) for 10 h gave N-(4-methoxybenzylidene)-1-(4-methoxyphenyl)methanamine **(94)** as a yellow oil (92 mg, 94%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.18 (s, 1H), 7.60 (d, 2H, J=8.6), 7.16 (d, 2H, J=8.6), 6.86-6.75 (m, 4H), 4.63 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H).

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161. 6, 161.0, 158.6, 131.5, 139.8, 129.0, 128.9, 114.1, 113.7, 64.3, 55.3, 55.1

Data in accordance with that previously published[55].

N-(3-methoxybenzylidene)-1-(3-methoxyphenyl)methanamine



(97)

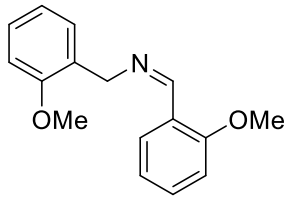
Following General Procedure A using 2-methoxybenzylamine (110 µL) for 10 h gave N-benzylidene- 1-phenylmethanamine **(97)** as a yellow oil (101 mg, 96%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.43 (1H, s), 7.49 – 7.42 (m, 1H), 7.39 – 7.25 (m, 3H), 7.01 – 6.76 (m, 3H) 4.71 (2H, s), 3.85 (s, 3H), 3.81 (s, 3H).

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161.92, 159.9, 159.7, 136.15, 136.0, 128.6, 128.3, 121.8, 120.3, 117.6, 113.5, 112.4, 111.5, 64.8, 55.3, 55.1

Data in accordance with that previously published[55].

N-(2-methoxybenzylidene)-1-(2-methoxyphenyl)methanamine



(98)

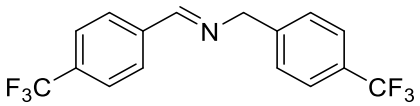
Following General Procedure A using 2-methoxybenzylamine (100 µL) for36 h gave N-(2-methoxybenzylidene)-1-(2-methoxyphenyl)methanamine **(98)** as a yellow oil (78 mg, 81%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.76 (s, 1H), 8.01 (dd, 1H, J = 7.6, 1.7 Hz), 7.34 – 7.09 (m, 3H), 7.02 – 6.71 (m, 4H), 4.72 (s, 2H), 3.76 (s, 3H), 3.76 (s, 3H).

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 160.0, 158.2, 157.2, 131.7, 129.1, 128.3, 127.9, 127.5, 124.8, 120.7, 120.8, 120.5, 111.0, 110.1, 59.7, 55.4, 55.3

Data in accordance with that previously published[55].

N-(4-(trifluoromethyl)benzylidene)-1-(4-(trifluoromethyl)phenyl)methanamine



(100)

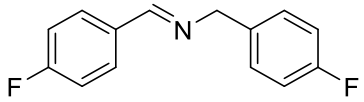
Following General Procedure A using 4-(trifluoromethyl)benzylamine (120 µL) for 24 h gave N-(4-(trifluoromethyl)benzylidene)-1-(4-(trifluoromethyl)phenyl)methanamine **(100)** as a yellow oil (112 mg, 97%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.47 (s, 1H), 7.92 (d, 2H, J = 8.0 Hz), 7.74 – 7.55 (m, 4h), 7.47 (d, 2H, J = 8.1 Hz) 4.92 (s, 2H)

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161.2, 143.2, 139.1, 133.0, 132.5, 128.6, 128.5, 125.6 (q, $J_{C,F}$ = 3.8 Hz), 125.4 (q, $J_{C,F}$ = 3.8 Hz), 122.4, 64.3

Data in accordance with that previously published[55].

N-(4-fluorobenzylidene)-1-(4-fluorophenyl)methanamine



(101)

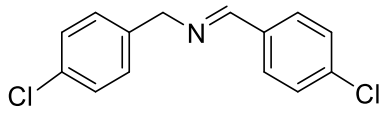
Following General Procedure A using 4-fluorobenzylamine (100 µL) for 24 h gave N-(4-fluorobenzylidene)-1-(4-fluorophenyl)methanamine **(101)** as a yellow oil (92 mg, 94%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.28 (1H, s) 8.28 (s, 1H), 7.75 - 7.63 (m, 2H), 7.25 - 7.15 (m, 2H), 7.04 - 6.86 (m, 4H), 4.71 (s, 2H)

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 166.3, 163.5, 162.7, 160.5, 160.4, 135.1 (d $J_{C,F}$ 3,1Hz), 132.3 (d $J_{C,F}$ 3,1Hz), 130.2 (d $J_{C,F}$ = 8,8Hz),, 129.5 (d $J_{C,F}$ = 8,8Hz), 115.7 (d $J_{C,F}$ = 22.3Hz), 115.3 (d $J_{C,F}$ = 22.3Hz), 64.2.

Data in accordance with that previously published[55].

N-(4-chloroybenzylidene)-1-(3-chlorophenyl)methanamine



(102)

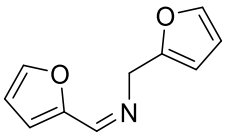
Following General Procedure A using 4-chlorobenzylamine (110 µL) for 18 h gave N-benzylidene- 1-phenylmethanamine **(102)** as a white solid (100 mg, 96%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.41 (1H, s), 7.66 (d, 2H, J = 8.5 Hz), 7.30 (d, 2H, J = 8.5 Hz), 7.26 – 7.16 (m, 4H), 4.75 (2H, s).

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161.1, 137.6, 137.2, 134.3, 132.8, 129.5, 129.1, 129.0, 128.6, 64.1.

Data in accordance with that previously published[55].

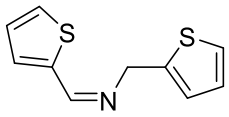
1-(furan-2-yl)-N-(furan-2-ylmethylene)methanamine



(103)

Following General Procedure A using furylamine (90 µL) for 10 h gave a solid that could not be dissolved in any deuterated solvent for analysis.

1-(thiophen-2-yl)-N-(thiophen-2-ylmethylene)methanamine



(104)

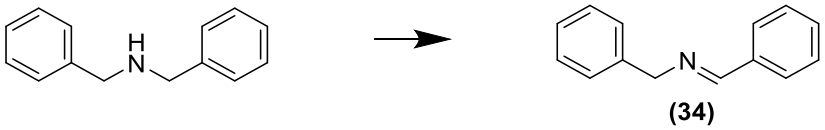
Following General Procedure A using thiophenemethylamine (105 µL) for 10 h gave N1-(thiophen-2-yl)-N-(thiophen-2-ylmethylene)methanamine **104** as a white solid (100 mg, 99%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.42 (s, 1H), 7.43 (dt, 1H, J = 4.8, 1.0 Hz), 7.35 (dd, 1H, J = 3.6, 1.0 Hz), 7.07 (dd, 1H, J = 4.8, 3.6 Hz), 7.05 – 6.95 (m, 2H), 4.95 (s, 1H).

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 155.4, 142.1, 141.4, 131.0, 129.3, 127.5, 127.4, 125.3, 124.8, 58.4

Data in accordance with that previously published[55].

N-benzylidene-1-phenylmethanamine



(34)

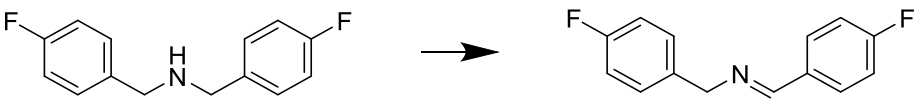
Following General Procedure A using dibenzylamine (200 µL) for 10 h gave N-benzylidene-1-phenylmethanamine **(34)** as an oil (192 mg, 96%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.42 (s, 1H), 7.783-7.74 (m, 2H), 7.50 – 7.23 (m 2H), 4.75 (s, 2H);

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161.9, 139.3, 136.2, 130.7, 128.6, 128.3, 127.9, 127.1, 65.00

Data in accordance with that previously published[55].

N-(4-fluorobenzylidene)-1-(4-fluorophenyl)methanamine



(101)

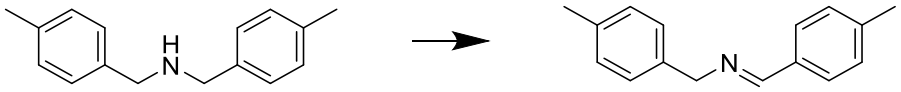
Following General Procedure A using di(4-fluorobenzyl)amine (200 µL) for 24 h gave N-(4-fluorobenzylidene)-1-(4-fluorophenyl)methanamine **(101)** as a yellow oil (193 mg, 97%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.28 (1H, s) 8.28 (s, 1H), 7.75 - 7.63 (m, 2H), 7.25 - 7.15 (m, 2H), 7.04 - 6.86 (m, 4H), 4.71 (s, 2H)

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 166.3, 163.5, 162.7, 160.5, 160.4, 135.1 (d $J_{C,F}$ 3,1Hz), 132.3 (d $J_{C,F}$ 3,1Hz), 130.2 (d $J_{C,F}$ = 8,8Hz),, 129.5 (d $J_{C,F}$ = 8,8Hz), 115.7 (d $J_{C,F}$ = 22.3Hz), 115.3 (d $J_{C,F}$ = 22.3Hz), 64.2.

Data in accordance with that previously published[55].

N-(4-methylbenzylidene)-1-(p-tolyl)methanamine



(93)

Following General Procedure A using di-(4-methylbenzyl)amine (210 µL) for 10 h gave N-(4-methylbenzylidene)-1-(p-tolyl)methanamine **(93)** as a white solid (200 mg, 98%).

$_1$H-NMR: (300 MHz) ($CDCl_3$) δ_H = 8.41 (s, 1H), 7.63 (d, 2H, J=8.1), 7.19-7.01 (m, 6H), 4.67 (s, 2H), 2.34 (s, 3H), 2.30 (s, 3H)

$_{13}$C-NMR: (75 MHz) ($CDCl_3$) δ_C = 161.9, 139.3, 136.2, 130.7, 128.6, 128.3, 127.9, 127.1, 65.00, 36.2, 36.0

Data in accordance with that previously published[55].

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